CHAPTER

54 Systemic Sclerosis, Rheumatoid Arthritis, Sjögren Syndrome, and Polymyositis and Dermatomyositis

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SYSTEMIC SCLEROSIS (SCLERODERMA)

Scleroderma is a broad, often confusing, term that encompasses a subset of chronic connective tissue diseases resulting from the overproduction and accumulation of collagen and other extracellular matrix proteins. Derived from the Greek word sklēros, meaning hard, and derma, meaning skin, scleroderma describes the hardened skin that is the hallmark clinical feature of this disorder. However, the disease is far more complex than this term implies. As such, scleroderma is now classified into two accepted disease subsets, morphea and systemic sclerosis (SSc), which more accurately reflect the broad range of clinical features seen in this disease.[1,2] Morphea, the localized form of scleroderma, is limited to the skin and generally carries a favorable prognosis with normal life expectancy. On the other hand, SSc, a widespread disorder with internal organ involvement, is generally associated with a worse prognosis and significant disability and mortality.

SSc is characterized by intense uncontrolled fibrosis of the skin, subcutaneous tissues, and organs (most notably the kidneys, lungs, gastrointestinal tract, and heart), accompanied by a proliferative and obliterative vasculopathy. There is considerable heterogeneity in the clinical manifestations and severity of SSc. Two well-recognized clinical subsets of SSc, the limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) forms, are used to further subclassify patients based on the extent and distribution of skin involvement. Autoantibody profiles, patterns of internal organ involvement, and prognosis differ considerably between the groups. The limited form, which primarily affects the skin distal to the elbows and knees, is typically associated with Raynaud phenomenon, telangiectasia, and gastrointestinal involvement as part of the CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia). Pulmonary hypertension and anticentromere antibodies are more common in this disease subset. Diffuse SSc is associated with more extensive sclerosis involving the skin proximal to the elbow and knee flexures or the trunk and earlier onset of internal organ involvement. Antitopoisomerase I and anti-RNA polymerase III antibodies are frequently present. Patients with dcSSc are at increased risk of developing the devastating complication, scleroderma renal crisis, discussed in the following paragraphs.

Epidemiology

Although there are conflicting estimates of prevalence and incidence of SSc, it is known that it is relatively uncommon compared to other connective tissue diseases. Prevalence estimates range from 7 to 489 cases per million persons and an incidence range from 0.6 to 122 cases per million persons per year (for comparison, prevalence of lupus ranges from 200 to 1500 cases per million persons).[3,4] The wide range in reported estimates between studies reflects a multitude of factors including different diagnostic definitions, inclusion of different subtypes of disease, data acquisition strategies, geographic variation, and study methods and design. The average disease onset is between the fourth and fifth decades. There is a female predominance with a female to male ratio ranging from 3:1 to 8:1, and it is almost twice as common in blacks as in whites.

Pathogenesis

The events that lead to the systemic fibrosis, microvascular damage, and immune dysregulation that are characteristic of SSc are only partially understood. Collectively, the body of evidence supports a multistep process involving a complex interplay between the vascular system, the immune system, and the extracellular matrix. This occurs in the context of a unique genetic susceptibility[5] and possible environmental stimuli.[6,7] Although a detailed discussion of disease pathogenesis is beyond the scope of this chapter, important concepts will be highlighted here. For a more detailed discussion, we refer the reader to several recent excellent reviews.[8–11]

Injury to the vascular endothelium, primarily of small vessels, is an important proximal event preceding the development of fibrosis.[12] The inciting factor remains unknown, though numerous environmental and infectious agents have been suggested. There is significant evidence that mechanisms of vascular remodeling, needed to restore vessel integrity and

function after this initial injury, are abnormal in SSc. This adverse remodeling leads to pathologic intimal proliferation and medial hypertrophy, culminating in luminal narrowing (or obliteration) and tissue ischemia.[13] The abnormally thickened vessel walls promote intravascular thrombosis from platelet aggregation and further contribute to luminal narrowing. Angiogenesis and vasculogenesis also appear dysregulated in SSc, leading to vascular malformations and an impaired ability to generate new functional microvessels.[10]

Functional abnormalities of the vascular system are superimposed on structural abnormalities.[13] Vascular instability and altered vasoreactivity are prominent features in SSc and further compromise the vascular compartment.[10] An imbalance between vasoconstrictive and vasodilating mediators plays a role. Endothelin 1 (ET-1), released by injured endothelial cells, has received much attention in this regard. ET-1 is not only a potent vasoconstrictor but is also known to be profibrogenic, enhancing fibroblast proliferation and collagen synthesis. Thus, ET-1 may be an important link between the observed vasculopathy and pathologic fibrosis.

Tissue fibrosis dominates the second phase of this disease.[8] Persistent and uncontrolled upregulation of collagen gene expression by recruited fibroblasts and myofibroblasts leads to excessive deposition of collagen and other extracellular matrix (ECM) proteins. Complex autocrine and paracrine signaling loops sustain and amplify the abnormal fibrogenic response. Some of the relevant mediators in the signaling loops include the cytokines interleukin (IL)-1, IL-2, IL-4, and IL-6, activating factors such as transforming growth factor beta (TGF-β), platelet-derived growth factor and connective tissue growth factor, and monocyte chemotactic protein-1.[9] There is also increasing recognition that tissue hypoxia, which occurs in the context of the aforementioned vascular abnormalities, perpetuates the cycle of fibrosis and vascular pathology. Several mechanisms have been postulated: (1) hypoxia stimulates the production of extracellular matrix proteins via hypoxia-inducible factor-1 α-dependent and α-independent pathways; (2) hypoxia is also a potent inducer of vascular endothelial growth factor (VEGF), which when chronically overexpressed, leads to the formation of chaotic vessels with decreased blood flow.[14,15] Thus, hypoxia may be another link between vasculopathy and fibrosis in SSc.

Although it is generally accepted that autoimmunity has a role in disease pathogenesis, many issues remain unresolved.[8,12] It is unclear whether immune dysfunction is involved in initiation and/or disease maintenance. It is also not clear how the pathways of vascular pathology, fibrosis, and autoimmunity intersect. Numerous disturbances of both the humoral and cell-mediated immune systems have been described in different subsets of SSc patients at varying stages of the disease with different clinical manifestations.[9] Conflicting and inconsistent reports regarding these immune abnormalities (related in part to the heterogeneity of the populations studied) have led to difficulty with the interpretation of such findings and uncertainty regarding their relevance. Nevertheless, considerable evidence indicates that a skewed balance between type 1 and type 2 helper T cells toward Th2 activation is important for development of fibrosis. Emerging data also suggest that IL-17–producing T cells (Th17) may be relevant in pathogenesis.[9]

Numerous autoantibodies are also detected in the sera of SSc patients.[16] These include antinuclear antibodies such as antitopoisomerase 1 (anti-Scl 70) and anticentromere, as well as antinuclear antibodies (i.e., anti-RNA polymerase III and anti-U3-fibrillarin). Much is known about the associations of these antibodies with clinical subsets and patterns of organ involvement in SSc (i.e., anticentromere with limited SSc; anti-Scl 70 with diffuse SSs). However, to date, evidence that these autoantibodies are pathogenic has not been firmly established. More recently, several additional autoantibodies directed against nonnuclear antigens have been detected. These include antiendothelial cell antibodies, antifibrillin-1 antibodies, anti-matrix metalloproteinase antibodies, and antiplatelet-derived growth factor receptor antibodies.[17] Experimental evidence suggests that these antibodies may be relevant in disease pathogenesis by initiating and/or propagating tissue damage. However, confirmatory studies are needed.

Scleroderma Renal Crisis

Scleroderma renal crisis (SRC) is one of the most devastating and life-threatening complications of systemic sclerosis. It develops in 5% to 10% of SSc patients and is seen almost exclusively in patients with diffuse systemic sclerosis. Two large cohort studies reviewed the clinical characteristics of SSc patients who develop this renal complication.[2,18] Penn et al.[18] described the course of 1997 SSc patients seen at a single institution between 1990 and 2005 and reported that 110 (5.5%) developed SRC. Of these, 86 patients (78%) had diffuse disease and 24 (22%) had limited disease. These data are comparable to those of other studies.

Scleroderma renal crisis usually develops early in the course of the disease. Approximately two thirds of affected patients carry the diagnosis of SSc for less than 1 year and almost all SRC cases are diagnosed within 5 years of the onset of SSc. Patients typically present with a precipitous onset of severe hypertension and rapid deterioration of renal function with oliguria or anuria. This is often accompanied by signs of microangiopathic hemolysis. Clinical manifestations of SRC are mainly those of malignant hypertension (e.g., headache and/or seizures from hypertensive encephalopathy and visual disturbances from hypertensive retinopathy). Dyspnea may be due to acute left ventricular failure and pulmonary edema due to the effects of malignant hypertension on the myocardium and volume overload from oliguria. Associated laboratory findings include elevated serum creatinine that progressively and rapidly rises and may be accompanied by proteinuria, which is usually in the subnephrotic range (<2.5 g per 24 hours). Nephrotic range proteinuria is uncommon. Urine sediment may be normal or may reveal microscopic hematuria with few cells or casts but a nephritic sediment is unusual. Anemia, thrombocytopenia, and schistocytes in the peripheral blood smear support the presence of a microangiopathic hemolytic process along with other

markers of intravascular hemolysis such as elevated lactate dehydrogenase (LDH) and low haptoglobin.

Atypical presentations may make the syndrome more difficult to recognize, leading to missed diagnoses. Normotensive renal crisis occurs in 10% of cases of SRC.[19] Although blood pressures are normal or only modestly elevated in this variant of renal crisis, they are often higher than the patient's baseline blood pressure. This subtle change can serve as an important clue to the diagnosis and underscores the need to closely monitor blood pressures in SSc patients (particularly those at a high risk of SRC). Thrombotic microangiopathy is often present in normotensive SRC and its presence should also raise suspicion of this syndrome.[20] Renal crisis can also occur rarely in a subset of patients who have no significant dermal sclerosis (referred to as sclerosis sine scleroderma). These patients have characteristic internal organ involvement but an absence of detectable skin features. Finally, in one quarter of patients, the diagnosis of SRC will precede a formal diagnosis of systemic sclerosis.[18,21]

One of the challenges in diagnosing SRC, in both typical and atypical presentations, is distinguishing it from other forms of thrombotic microangiopathy (i.e., thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [TTP/HUS]) given the similarities in presentation and laboratory abnormalities. This distinction is important as therapies differ. A renal biopsy does not reliably distinguish between these disorders. Rather, the clinical diagnosis relies on a compatible history, an evaluation of appropriate serologies, and a careful assessment of risk factors. Several factors may help to identify patients at a greater risk of developing SRC.[22] These include early diffuse systemic sclerosis, rapidly progressive skin thickening, new onset anemia, and new cardiac events (such as heart failure or pericardial effusion). Use of glucocorticoids (≥15 mg per day or the equivalent) in the preceding 6 months have long been considered a potential precipitant in SRC. In a case control study, Steen and Medsger[23] reported that high dose corticosteroids were administered more frequently in SRC patients (36%) than in controls (12%) (odds ratio [OR], 4.37). Although this association has also been reported by other investigators, causality is difficult to prove.[21] Rather, corticosteroids may have a confounding role because patients who are most likely to receive corticosteroids are also those at the highest risk for SRC. Nevertheless, the avoidance of corticosteroids in patients at risk is prudent. Autoantibody profiles may also provide clues regarding the risk of SRC. Anti-RNA polymerase III antibodies are associated with the development of SRC. Antifibrillarin or anti-U3-RNP antibodies may also identify patients at risk of developing internal organ manifestations, including SRC.[24] Conversely, patients with anticentromere antibodies are less likely to develop SRC.[18]

Pathophysiology of Scleroderma Renal Crisis

Injury to vascular endothelial walls, which underlies the pathophysiology of SSc in general, is considered a primary event in SRC. The vascular insult in SRC occurs in the interlobular and arcuate arteries of the renal cortex. The resulting thickening and proliferation of the intima, the deposition of glycoproteins and mucopolysaccharides, and the formation of platelet microthrombi lead to luminal narrowing and reduced renal perfusion. Chronic renal cortical ischemia leads to hyperplasia of the juxtaglomerular apparatus, stimulation of renin release, and activation of the renin-angiotensin-aldosterone system (RAAS). Hyperreninemia and ongoing activation of the RAAS is well recognized as playing a pivotal role in SRC by perpetuating intrarenal vasoconstriction, exacerbating renal ischemia, and inducing hypertension.[25] However, RAAS activation alone appears insufficient to initiate the full expression of SRC. Indeed, investigators have found that plasma renin levels can be markedly elevated for some time prior to the onset of SRC and may even be seen in patients that do not develop SRC.[26] Thus, an additional trigger(s), superimposed on a system "primed" by renin excess, is believed necessary to set in motion the explosive cascade of events of SRC. This trigger is unknown, but it has been proposed that conditions or stimuli that acutely compromise renal perfusion such as dehydration, sepsis, cardiac dysfunction, or intense vasospasm of intrarenal arterioles (possibly from cold exposure or other stressors) may contribute.[26–28]

Dysregulation in the endothelin system has also been implicated in the pathophysiology of SRC. Levels of ET-1 are increased in SSc patients with renal crisis.[29,30] One pathology study compared the distribution of ET-1 (by immunohistochemistry) in renal biopsies from SRC patients and patients with other vascular diseases involving the kidney.[31] Increased expression of both ET-1 and ET-1 receptors was detected in the small renal arteries of SRC patients, and the pattern of endothelial staining for ET-1 in both glomeruli and arteriolar lesions appeared specific for renal crisis.

The Role of a Renal Biopsy

A renal biopsy is usually not required to establish the diagnosis of SRC. Histologic changes are not pathognomonic for SRC and can be seen in other conditions that share endothelial injury as an underlying mechanism, such as malignant hypertension, TTP/HUS, and antiphospholipid syndrome. A renal biopsy is warranted when there is diagnostic uncertainty and/or to exclude other pathologies that warrant different management, such as crescentic glomerulonephritis or other inflammatory glomerular diseases.

The pathologic changes of SRC are evident in the small interlobular and arcuate arteries.[32,33] There is edema and thickening of the intima from mucin accumulation, and the characteristic onion skin lesion is due to concentrically arranged myointimal cellular proliferation and fibrosis, as shown in Figure 54.1. Both contribute to a luminal occlusion. Thrombosis and fibrinoid necrosis may be seen. The juxtaglomerular apparatus may appear particularly prominent, which is consistent with hyperreninemia from a reduced renal perfusion. Glomerular changes are variable and may be related to renal ischemia or direct glomerular endothelial injury. There may be a collapse of capillary loops or a thickening of

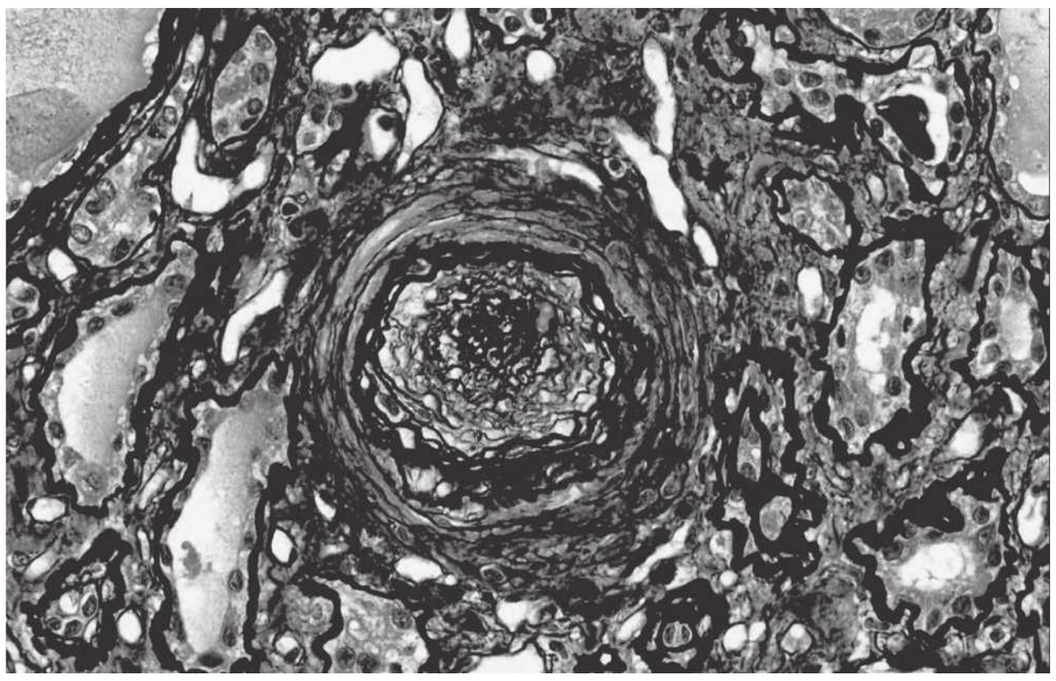


FIGURE 54.1 Scleroderma renal crisis, advanced stage. A methenamine silver stain of severe vasculopathy in a small arcuate artery compromised by luminal narrowing resulting from endothelial damage and the formation of concentric rings of myointimal fibrosis (onion skinning). (Biopsy specimen provided by Dr. Mark Haas, Renal Pathology Service, Cedars-Sinai Medical Center, Los Angeles, CA.)

capillary walls with a double contour appearance (on silver or periodic acid Schiff [PAS] staining), which are due to fibrin thrombi. Immune complexes are not present.

Treatment of Scleroderma Renal Crisis

Early diagnosis and prompt, aggressive treatment with ACE inhibitors (ACE-I) is crucial to prevent irreversible renal damage and a potentially fatal course. The effectiveness of ACE-I in halting progression and even reversing the process may be attributed to the interruption of the renin-angiotensin system, and AT-II–induced vasoconstriction. The angiotensin-converting enzyme also degrades bradykinin, a potent vasodilator. Interfering with this degradation of bradykinin may also contribute to the positive effects of ACE-I.

Most experience in SRC is with captopril, the agent used in early studies. There are fewer data available regarding the efficacy of other ACE-I in this setting, but they likely provide comparable benefit. Nevertheless, advantages of captopril in the acute setting include a rapid onset of action and a short duration of action, which provide more flexibility for dose titration. Captopril is usually initiated at 6.25 to 12.5 mg every 8 hours. The dose is titrated up (to 50 mg three times daily) to achieve gradual but steady blood pressure reduction. The goal is to return the patient to baseline blood pressures within 72 hours. Some recommend that blood pressure reductions should not exceed 20 mm Hg per 24 hours because this may compromise renal perfusion and should increase the risk of acute tubular necrosis. Even with judicious control of blood pressure, serum creatinine may rise with ACE-I therapy because of the associated decrease in efferent arteriolar resistance and intraglomerular pressure. However, this is not an indication for the discontinuation of therapy. Treatment with ACE-I is also indicated for patients with normotensive renal crisis, but escalation should be done carefully to avoid hypotension.

Data regarding the efficacy of AT-II receptor blockers (ARB) for the initial management of SRC are less clear. Some have reported benefit; others suggest suboptimal blood pressure control and greater rates of renal failure in patients with SRC treated with ARBs alone and subsequent improvement in renal function with the substitution of ACE-I.[34] The reason for such differences is unknown, but a possible explanation may be that ARBs, unlike ACE-I, do not inhibit the degradation of bradykinin.

If ACE inhibitors (at maximum recommended doses) are not sufficient to lower the blood pressure, other antihypertensive agents should be added. There are no studies that address which agents are most effective in this setting. Diuretics are best avoided (unless there is a strong clinical indication) because they may stimulate renin level. β-Blockers have the theoretic potential to worsen Raynaud phenomenon. Thus avoidance, if possible, might be prudent. Calcium channel blockers and vasodilators are reasonable options. Blocking the RAAS at multiple sites is an attractive approach in SRC. Aliskiren, a direct renin inhibitor, has theoretic benefit to further attenuate the RAAS in SRC and lower blood pressure. By blocking the catalytic activity of renin at the point of activation of the RAAS, aliskiren blocks the synthesis of all angiotensin peptides. This prevents the compensatory increase in renin that can be seen with ACE-I and ARB. At present, no studies have explored direct renin inhibition for therapy of SRC.

Despite the overall impressive impact of ACE-I on disease course, individual responses vary and many patients still suffer the full expression of SRC. The extent of this problem is highlighted in studies by Steen and Medsger[35] and Penn et al.,[18] which reviewed the course of SRC patients treated immediately (and aggressively) with ACE inhibitors. Permanent dialysis was required in 20% and 41% of these patients, respectively. This underscores the need for additional therapeutic strategies (beyond blockade of the RAAS) for this devastating complication. Intravenous prostacyclin and its analog, iloprost, have been used at some centers during the hypertensive phase of the renal crisis based on anecdotal observations of benefit.[36,37] Prostacyclin mediates vasodilation and has been reported to increase renal perfusion. There are no formal trials addressing the role of prostanoids as adjunctive therapy to angiotensin converting enzyme [ACE-I] in SRC.[37] HMG-CoA reductase inhibitors (statins) have been proposed for the treatment of SRC and possible prophylaxis.[38] This is based on evidence suggesting that statins may have a direct protective effect on endothelium, in addition to their well-known cholesterol lowering effect. ET is also a potential target of interest. The use of ET receptor antagonists in SRC is a particularly compelling idea in light of the possible role of ET in this disorder. Apart from their vasodilating effects, ET receptor antagonists may also reduce the profibrotic effects of endothelin. Data regarding the use of ET-receptor antagonism in SRC are limited. In a small

pilot study, six patients with SRC were treated with bosentan, a nonselective ET-receptor antagonist, within 6 weeks of their diagnosis.[38a] All patients were also receiving ACE-I at full therapeutic doses. The treatment regimen consisted of bosentan at 62.5 mg for 1 month and then 125 mg twice daily for 5 months. Bosentan was well tolerated. Overall, mortality and dialysis rates were not significantly different compared to a historic cohort receiving standard therapy. Rebound phenomena (i.e., Raynaud phenomenon, hypertension), occurred in half of the patients upon the withdrawal of therapy. A larger, open label trial using bosentan is currently recruiting in France to more fully assess efficacy of this drug in SRC. (clinical trials.gov: Effect of Bosentan in Scleroderma Renal Crisis/ScS-REINBO)

Prognosis

Prior to the availability and aggressive use of ACE inhibitors, the prognosis of SRC was abysmal with progression to end stage kidney disease (ESKD) over a period of 1 to 2 months and death usually within 1 year. The benefits of ACE-I in SRC were supported in an early single center study by Steen et al.,[39] which compared outcomes before and after the availability of ACE-I. One-year survival improved from 15% to 76% after the introduction of ACE-I therapy. Five-year survival improved from 10% to 65% with treatment. No randomized controlled trials have performed a head-to-head comparison of other therapies versus ACE-I and, given the evidence, there likely will never be.

In patients who do not require dialysis during their course of SRC, improvements in renal function are detectable for several years, suggesting that recovery is a slow, prolonged process that likely includes vascular remodeling.[18] Among patients who require renal replacement therapy during the acute episode of SRC, more than half may recover sufficient renal function to permanently discontinue dialysis within 12 to 18 months.[35] The continuation of ACE inhibitors is recommended during dialysis while monitoring for signs of renal recovery. Long-term survival of patients who never require dialysis or only need temporary dialysis seems to be comparable to patients with diffuse disease without a renal crisis. In contrast, long-term survival is less favorable for patients who remain dialysis dependent. These patients appear to have a higher mortality compared to those with end-stage kidney disease for other reasons.

It is noteworthy that the prognosis of patients with normotensive SRC appears worse than in hypertensive patients.[20] The basis for this is unclear, but hypotheses have been proposed. Difficulty in recognizing SRC in an atypical form may lead to a delay in diagnosis and management, allowing ongoing subclinical injury that may be irreversible. Alternatively, different pathogenetic mechanisms may underlie this form of SRC, which may be less dependent on the activation of the RAAS and thus, less responsive to ACE inhibitors. Other risk factors associated with a poor outcome in SRC include male sex, older age, the presence of congestive heart failure, serum creatinine levels greater than 3 mg per deciliter at the initiation of treatment, and a time period of more than 3 days to control blood pressure.[35,39]

Renal Transplant

A renal transplant is an acceptable option for those who progress to end-stage kidney disease and who fail to recover renal function due to SRC. Transplantation may offer a survival advantage compared to patients who remain on dialysis.[40] However, in light of the potential for delayed renal recovery, decisions regarding renal transplantation should be deferred for at least 2 years. Renal allograft outcomes are reasonable, although they may be reduced compared to the general renal transplant population.[40,41]

Recurrence of SRC is a concern but is uncommon. It is estimated to occur in less than 5% of cases.[42] Most of the reported cases recurred relatively early in the posttransplant course within 2 years. Establishing the diagnosis of recurrent SRC in the allograft can be particularly challenging because other processes such as acute antibody mediation rejection, chronic transplant vasculopathy, and acute calcineurin inhibitor nephrotoxicity produce a similar histologic appearance. To reduce the risk of recurrent disease, high dose glucocorticoids should be used judiciously given their potential role in precipitating a renal crisis. When unavoidable, limiting the dose and duration is recommended. Calcineurin inhibitors have also been associated with precipitating renal crises in case reports. Thus, it may be prudent to consider alternative immunosuppressants.

Monitoring and Prevention

The unpredictable onset of SRC and the importance of a prompt diagnosis underscores the necessity of careful monitoring of SSc patients, particularly those considered at the highest risk for this complication. Educating patients about symptoms and signs of SRC is important, and consistent home blood pressure monitoring should be encouraged.

Prophylactic use of ACE-I or ARB do not appear to protect against the development of SRC.[21,23] Retrospective and case control studies have found neither benefit nor harm with ACE inhibitors related to the development of SRC,[23] although some investigators have noted a trend toward worse renal outcomes.[18,21] Further investigations are needed to clarify these findings.

Antineutrophil Cytoplasmic Antibody–Associated Renal Disease

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is another distinct cause of rapidly progressive renal failure in SSc patients. The concurrence of AAV and SSc is a relatively rare complication described only in case reports and small cases series.[43–46] Nevertheless, AAV is an important entity to consider in the differential diagnosis of acute kidney injury in SSc patients and needs to be distinguished from SRC, which may have a similar clinical presentation but a completely different therapeutic approach.

AAV can occur in both the diffuse and limited variants of SSc, and it has also been reported in patients with systemic sclerosis sine scleroderma.[47,48] It is most common in the fifth and sixth decade of life and has a similar gender distribution as all SSC patients (female to male ratio, 4:1). Nearly all SSc patients with concurrent AAV have ANCAs with a perinuclear staining pattern (p-ANCA) directed against myeloperoxidase (MPO-ANCA). Clinical manifestations are more consistent with microscopic polyangiitis rather than granulomatosis with polyangiitis (Wegener granulomatosis). ANCAs directed against PR3 ANCA are rarely detected in this population.[49]

Certain presenting clinical and laboratory features may help to distinguish AAV from SRC (Table 54.1).[44,46] ANCA-associated kidney disease tends to occur later in the course of SSc, whereas SRC generally occurs earlier. The average duration of SSc prior to the onset of AAV and SRC is 7.8 years and 3.2 years, respectively. In contrast to SRC, which is associated with severe hypertension, blood pressure in ANCA-related acute kidney injury tends to be normal, although mild-to-moderate hypertension may be present in up to one third of patients. As such, AAV may be confused with and misdiagnosed as normotensive SRC. Patients with AAV in the context of SSc may present with other manifestations of vasculitis including limb ischemia, cutaneous lesions, and neuromuscular involvement (i.e., mononeuritis multiplex). The presence of such findings favors a diagnosis of AAV over SRC. Also, the vasculitis of AAV is an inflammatory vasculitis, whereas SSc is a noninflammatory vasculopathy. Thus, evidence of inflammation such as fever and elevated acute phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) favors a diagnosis of AAV rather than SRC. Pulmonary hemorrhage is a frequent vasculitic manifestation leading to respiratory distress in this setting (pulmonary renal syndrome). Distinguishing an alveolar hemorrhage from a pulmonary edema, which may occur in SRC, is often difficult because the symptoms and radiologic imaging may be similar. Anemia can be present in both, but is usually normochromic normocytic in AAV and microangiopathic in SRC. The urine sediment is active and nephritic in AAV but typically is bland in SRC.

If AAV is suspected, tests for ANCA and for anti-MPO and anti-PR3 by enzyme-linked immunosorbent assay (ELISA) are warranted, but results are usually not available in a timely manner. A kidney biopsy should be performed expeditiously

54.1 Differentiating Etiologies of Rapidly Progressive Kidney Injury in Systemic Sclerosis: Scleroderma Renal Crisis Versus Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

	Scleroderma Renal Crisis	ANCA-Associated Crescentic Glomerulonephritis
Timing during disease course	Early	Late
Blood pressure	Usually malignant, uncommon: normotensive	Normal-to-moderate elevation
Anemia	Microangiopathic	Normochromic
Urine sediment	Bland	Nephritic
Acute phase reactants	Normal	Elevated
Acute respiratory issues	Pulmonary edema, congestive heart failure	Alveolar hemorrhage
Renin levels	Markedly elevated	Normal
Histology	Intimal edema and thickening; onion skin lesion, narrowing of vascular lumens	Pauci-immune necrotizing and crescentic glomerulonephritis
Treatment	ACE inhibitors	Immunosuppression

ACE, angiotensin converting enzyme.

to confirm the diagnosis. A histology is consistent with pauci-immune necrotizing and crescentic glomerulonephritis.

The treatment of AAV requires aggressive immunosuppression consisting of induction with high dose corticosteroids and cyclophosphamide with or without plasma exchange, followed by maintenance immunosuppressive therapy. B-cell depletion with rituximab might also be considered. Although data are limited, there are no reported cases of steroids promoting the development of SRC during the treatment of AAV despite the theoretic risk. Because prognosis is so poor without therapy, intensive immunosuppression, including steroids, is recommended.

What predisposes some SSc patients to the development of a superimposed vasculitis is not known. In some cases, a hypersensitivity reaction to the medication, D-penicillamine, has been considered to be a trigger, but in the vast majority, a cause is not identified. ANCAs have also been detected (rarely) in the sera of unselected SSc patients during screening evaluations.[44,46,49–51] The significance of ANCA in SSc patients without clinically evident vasculitis is controversial. Some authors suggest that this finding is considered a red flag, indicating an inflammatory component to the underlying disease, whereas others have found no increased risk of renal disease or other vasculitic complications.[50]

Other Renal Manifestations in Systemic Sclerosis

Other renal abnormalities may occur in SSc patients that are not as overt or as dramatic as SRC or ANCA vasculitis. Estimates of kidney involvement in SSc vary widely based on different definitions of kidney injury and the markers of renal disease that are examined.[52–58] One report identified abnormal renal function (defined as creatinine ≥1.2 mg per deciliter) or proteinuria (defined as 3 or 4+ proteinuria on dipstick on two occasions) in 16% and 13%, respectively, of patients with dcSSc (without a history of SRC).[57] Over a mean follow-up of 10 years, only 2 of 546 patients in this cohort reached end-stage kidney disease, suggesting a benign clinical course for the vast majority. A greater percentage of patients are considered to be affected if more sensitive measures of GFR are used.[53] One study measured GFR using technetium 99mDTPA in 31 patients with normal serum creatinine and showed a reduction of GFR in 55% of patients, with 32% categorized as stage II chronic kidney disease (CKD) (60 to 89 mL per minute) and 23% as stage III (30 to 59 mL per minute).[55] When pathologic renal change at an autopsy is used as the criterion, approximately 60% of patients will have histologic evidence of kidney involvement, indicating that subclinical disease is relatively common in SSc.[52,58]

Renal involvement in SSc patients may be related or unrelated to the underlying disease process, other organ involvement (i.e., heart failure, pulmonary hypertension), or associated therapies (Table 54.2). Treatment with D-penicillamine, which had been used for years for the management of skin involvement in dcSSc, has been associated with renal injury and proteinuria.[59] Up to 20% of treated patients develop membranous nephropathy, which resolves with drug cessation.[60] Diffuse proliferative glomerulonephritis, pulmonary renal syndrome, drug-induced lupus syndrome, and ANCA-related vasculitis have also been reported to be associated with D-penicillamine treatment.[61,62] Due to its high rate of side effects, including renal toxicity and questionable therapeutic effect, penicillamine is now rarely used in the treatment of SSc.

54.2 Renal Manifestations in Systemic Sclerosis

- Prerenal associated with cardiac or pulmonary artery involvement (heart failure, pulmonary hypertension), diuretics, NSAIDs
- Scleroderma renal crisis
- Glomerulonephritis
  - ANCA-associated crescentic glomerulonephritis
  - Penicillamine-induced renal injury
  - Overlap syndrome (i.e., with lupus or other connective tissue diseases)
- Chronic hypertension
- Decreased renal plasma flow,[54] higher renal vascular resistance[56]

NSAIDs, nonsteroidal anti-inflammatory drugs; ANCA, antineutrophil cytoplasmic antibody.

An important association exists between the presence of pulmonary hypertension and a reduced glomerular filtration rate. Campo et al.[63] evaluated 76 SSc patients with pulmonary arterial hypertension and reported that 45.6% had renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) at the time of diagnosis.[63] Only 6.5% of these patients had a prior episode of renal crisis. eGFR was a strong predictor of survival in this cohort, with an eGFR less than 60 mL/min/1.73 m^2 associated with a threefold risk of mortality. The reduction in GFR may reflect simultaneous structural damage to both the pulmonary and the renal vascular beds, or may be related to the prerenal effects of severe pulmonary hypertension.

Other studies have identified proteinuria as an independent risk factor for death in SSc patients with a hazard ratio of 3.34.[64–66] Although the mechanism for this association is not clear, it has been proposed that the presence of proteinuria may be a marker of more severe underlying endothelial dysfunction, which could portend a worse prognosis.

Novel Therapies for Systemic Sclerosis and the Potential for Renal Injury

Nonselective immunosuppressive medications (i.e., cyclophosphamide, azathioprine, prednisone, methotrexate) are frequently used to treat the complications of SSc despite a

lack of convincing data that these therapies reverse the natural disease progression.[67] Therapeutic attempts at selectively blocking fibrotic pathways have not met with much success, probably because of the complexity of the fibrotic process with its multiple layers of regulation. A number of newer biologic agents targeting other molecular pathways, cellular effectors, and signaling molecules believed to be operative in SSc are now available and are under clinical investigation.[68]

Autologous hematopoietic stem cell transplantation (HSCT) has also been applied for selected SSc patients with a poor prognosis (predominantly with diffuse cutaneous disease and severe internal organ involvement).[69] The rationale for HSCT in SSc is to reset the dysregulated immune system. Phase I/II trials of HSCT have demonstrated a reversal of skin fibrosis, improved functionality and quality of life, and stabilization of the internal organ function in SSc patients.[70–74] Experience is still limited and toxicity remains a concern. The potential for renal complications in SSc patients deserves special consideration.

Acute kidney injury (AKI) is not an uncommon complication after HSCT irrespective of the transplant indication. Kidney injury may manifest as thrombotic microangiopathy, radiation nephritis, glomerular disease, and acute tubular necrosis (ATN) (among others) and may be attributed to such factors as conditioning regimens, total body irradiation (TBI), nephrotoxic drugs (i.e., calcineurin inhibitors), and infections. Whether having SSc, with the associated underlying vasculopathy, conveys a higher risk of kidney injury after HSCT, particularly if exposed to radiation (which has effects on vascular endothelium), glucocorticoids, or calcineurin inhibitors, is unclear. Furthermore, both TMA and radiation nephritis can clinically mimic SRC. Distinguishing among these causes of AKI can be particularly challenging in SSc patients after HSCT. Until further data are available, measures to minimize nephrotoxicity will be important. These include aggressive control of blood pressure, the restricted use of glucocorticoids and calcineurin inhibitors, the avoidance of TBI or renal shielding, and close monitoring of renal function.

Presently, there are three ongoing randomized trials investigating the safety and efficacy of autologous HSCT for SSc: Autologous Stem Cell Transplantation International Scleroderma (ASTIS), American Systemic Sclerosis Immune Suppression Versus Transplant (ASSIST), and Scleroderma Cyclophosphamide Versus Transplant (SCOT). ASSIST and ASTIS use a nonmyeloablative regimen and SCOT uses a myeloablative regimen with total body irradiation. Hopefully, results from these trials will clarify the role of HSCT in SSc and will address the risk of kidney injury in these patients.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an inflammatory polyarthritis with a peak age of onset between 40 and 60 years and with a greater than twofold increased prevalence in women. RA is generally considered to represent an autoimmune disorder because of its characteristic laboratory profile of autoantibodies to cyclic citrullinated peptides (anti-CCP), to immunoglobulin G (rheumatoid factor), and to nuclear antigens (antinuclear antibodies [ANA]). There are numerous defects in cytokine production and cell-mediated immunoregulatory pathways that are integral components of the pathogenic inflammation and autoreactivity. Some investigators hypothesize, based on animal models and on epidemiologic evidence, that certain infections can be the triggering event, which in a susceptible person with genetically determined or otherwise acquired defects in immunoregulatory circuits leads to RA.[75]

Clinical Features of Rheumatoid Arthritis

RA is characterized by symmetrical stiffness and painful swellings (inflammation and effusions), typically of multiple joints of the upper and lower extremities; if these findings persist for more than 6 weeks, they fulfill a key diagnostic criterion for RA. Because RA typically progresses to a chronic disease, persistent or recurring synovitis leads to joint effusions and the destruction of cartilage and erosions of periarticular bone, eventuating in deforming arthropathies. Fatigability, malaise, anorexia, and weight loss are common debilitating features of RA, reflecting high circulating levels of immune complexes, acute phase reactants, and cytokines. The protracted inflammatory state, when not interdicted by effective disease remitting treatment, appears to be a major contributor to accelerated atherosclerotic cardiovascular disease, which in turn leads to increased rates of debilitating morbidity and premature mortality in patients with RA.[76]

General Treatment Strategies for Rheumatoid Arthritis

Multiple studies have shown definitively that destructive pathologic processes start very early in the course of RA, and that there are long-term benefits of aggressive therapy on the natural history of RA. In the acute stage of the disease, the clinical and laboratory manifestations of RA typically respond dramatically to corticosteroids. However, because it is unusual to find a nontoxic dose of corticosteroid that can provide sustained control of RA, alternative therapies have been intensely pursued. Historically, there has been a succession of agents used adjunctively with corticosteroids for the treatment of RA, including general anti-inflammatory drugs (e.g., salicylates, nonsteroidal anti-inflammatory drugs [NSAIDs], antimalarials, gold salts, penicillamine, sulfasalazine), as well as more potent and directly immunosuppressive agents (e.g., methotrexate, cyclophosphamide, azathioprine, leflunomide). These agents, categorized as disease-modifying antirheumatic drugs (DMARDs), have shown objective salutary effects on clinical manifestations and long-term complications of RA; however, none of these agents predictably or consistently induces complete remissions and most have had excessive adverse side effects when used as maintenance therapy. For example, gold salts and penicillamine have been largely abandoned as treatment for RA due to suboptimal efficacy and their propensity to cause secondary membranous nephropathy.

Weekly doses of oral methotrexate have been the stalwart therapy for long-term management of RA for the past 3 decades. Methotrexate and low dose corticosteroid combination therapy produces satisfactory remissions in a substantial majority of cases. However, for patients with refractory or relapsing disease, biologic agents that antagonize tumor necrosis factor (e.g., etanercept, infliximab, adalimumab) are added to the basal methotrexate regimen. Other agents under active investigation as adjuncts to methotrexate include rituximab, anti-IL6-receptor (tocilizumab), and the costimulation inhibitor, CTLA4-Ig.[77,78]

Kidney Involvement in Rheumatoid Arthritis

Abnormalities of kidney function (e.g., abnormal urinalysis, proteinuria, diminished glomerular filtration rate [GFR], abnormal pathology) were recognized several decades ago in up to half of patients with RA. These clinical laboratory abnormalities were attributed to poorly controlled RA (e.g., secondary amyloidosis) or to the complications of the limited options for symptomatic treatment of RA (e.g., interstitial nephritis due to the protracted use of high dose aspirin).[79,80] With subsequent availability of disease-modifying therapeutic strategies that provided more effective management of RA, the frequency of renal abnormalities has dramatically decreased and types of clinically significant renal complications have substantively changed over the past 2 to 3 decades. For example, both drug-induced interstitial nephritis and secondary amyloidosis have become increasingly rare due to the more effective treatment of RA. On the other hand, some types of glomerulonephritis do occur sporadically during the course of RA. The impacts on renal and patient survival of the different forms of glomerular disease vary from minor, in patients with isolated hematuria and low grade pathology, to major, in those with complicated nephritic and nephrotic syndromes and high grade pathology.[81]

Table 54.3 shows the range and weighted mean frequency of the main forms of kidney pathology occurring in renal biopsies from patients with RA as reported in four relatively large case series.[82–85] In rank order, mesangial proliferative glomerulonephritis, membranous nephropathy, and AA amyloidosis are the most frequent diagnoses, but there are several other nephropathies observed in patients undergoing a renal biopsy for clinical indications, including a very imposing and ominous form of renal vasculitis.

Mesangial Glomerulonephritis

Although mesangial proliferative glomerulonephritis accounts for approximately one third of cases, this may be an underestimate of its frequency, because isolated hematuria, following negative imaging studies of the upper and lower urinary tracts, is not universally considered an indication for a renal biopsy. Mesangial glomerulonephritis is associated with mesangial deposits of immune complexes. Because the mesangium is considered to be a normal channel of egress for at least some fraction of immune complexes from the circulation, it is likely that this pathway is simply overloaded in RA where there is an extremely heavy burden of circulating immune complexes (even if the immune complexes, per se, are characteristically of low intrinsic nephritogenicity). The mesangial proliferative glomerulonephritis associated with RA tends to be mild and has been shown in long-term follow-up studies to have a benign prognosis.[86]

Membranous Nephropathy

The emergence of proteinuria, particularly into the nephrotic range, heralds more clinically challenging glomerular diseases, most commonly membranous nephropathy or secondary AA amyloidosis. Mixed nephritic, nephrotic, and azotemic syndromes in the patient with RA may also indicate overlap-

54.3 Renal Biopsy Series in Patients with Rheumatoid Arthritis

		Percentage			
Author, yr [Ref]	**# Cases**	**Mes**	**MN**	**AA**	**Other**
Sellers et al., 1983[85]	30	43	30	3	23%
Adu et al., 1993[82]	10	20	50		30%
Helin et al., 1995[83]	110	36	17	30	7%
Nakano et al., 1998[84]	158	34	31	19	16%
Weighted mean (total # cases = 308)		35	27	21	14%

yr, year; Mes, mesangial glomerulonephritis; MN, membranous nephropathy; AA, amyloidosis. Other category includes lupus nephritis, renal vasculitis, IgA nephropathy, and interstitial nephritis.

ping rheumatic diseases. For example, some patients with RA have diagnostic features of both RA and systematic lupus erythematosus (SLE) (sometimes called rhupus). In this case, the manifestations and prognostic implications of SLE and lupus nephritis are likely to be of pre-eminent importance in the management of the patient with underlying RA. Patients with RA may also have features of a mixed connective tissue disease (MCTD), including Sjögren syndrome. However, the concurrence with RA of either MCTD or Sjögren syndrome rarely increases the likelihood of serious renal disease, aside from membranous nephropathy.

The etiopathogenesis of membranous nephropathy in any of the rheumatic diseases has not been determined, but it is likely to be related to the emergence of polyclonal antibodies with particular autoreactivity (or cross-reactivity) to constitutive antigens of the podocytes of the glomerular epithelial cell. An alternative hypothesis is based on the historical impression of a modestly increased frequency of membranous nephropathy in the context of sustained treatment of RA with gold salts[87] and penicillamine.[60] Based on experimental models, this hypothesis holds that exogenous agents may create autoreactivity after being bound or "planted" in the glomerular basement membrane or on the visceral epithelial cell. Thus, although there are numerous case series suggesting an association between the use of gold, penicillamine, or bucillamine and the emergence of membranous nephropathy in RA, it is clear that the risk of membranous nephropathy is associated with RA, per se.[61,88–92] The pathogenic role of these drugs to amplify the risk of membranous nephropathy in RA has never been fully resolved and, indeed, has become moot, because gold salts, penicillamine, or bucillamine are rarely used for the treatment of RA in current medical practice.

Initial approaches to membranous nephropathy discovered during the course of RA should be examined to discover whether there are cofactors (e.g., SLE, syphilis, hepatitis B, occult malignancy) that could be modified, as well as substituting alternative antirheumatic drugs for those that have been suspected to incite membranous nephropathy. Examining whether inadequate treatment for RA may also foster secondary membranous nephropathy is another consideration and may lead to modification of the treatment regimen for better control of RA. If no other contributing factors are identified, the treatment of membranous nephropathy occurring in the context of RA is basically governed by the same principles that apply to the treatment of idiopathic membranous nephropathy.

AA Amyloidosis

Patients with persistently active, unremitting RA are burdened with protracted inflammation and have high levels of acute phase reactants, including elevations of the serum amyloid A (SAA) protein, which predispose them to secondary or AA amyloidosis (Fig. 54.2).[93] Some autopsy surveys have shown that AA amyloidosis can be subclinical and that small amounts of amyloid deposits may be detectable in more than one quarter of the autopsies of RA patients.[94] Risks of developing amyloidosis associated with RA also increases in the setting of poor access to medical care, as well as the historical inclination of many physicians to administer disease-modifying agents for RA in a "go low and go slow" fashion. Older age of onset of RA also predisposes a patient to an increased risk of AA amyloidosis.[95]

AA amyloidosis characteristically affects the kidney where glomerular deposits of amyloid produce proteinuria and arterial deposits further contribute to decreased renal function. Gastrointestinal tract involvement is equally frequent, and debilitating gut malabsorption syndromes may precede or emerge concurrently with manifestations of renal amyloidosis. AA amyloidosis of the kidney has a significant impact on patient survival.[81]

Numerous studies over the past few years have demonstrated the long-term benefits of aggressive early treatment of RA both in preventing deforming arthropathy and systemic complications such as AA amyloidosis, as well as decreasing the rates of progression to end-stage renal disease[96] and mortality from accelerated cardiovascular disease.[78] Fortunately, the incidence of AA amyloidosis as a complication of uncontrolled RA has been steadily decreasing in the setting of early intervention with the armamentarium of modern treatment options for RA.

The development of amyloidosis during the course of RA should prompt a critical reassessment of whether the treatment regimen has been on goal based on objective measures of the disease activity of RA because interdiction of the dire consequences of AA amyloid depends mostly on comprehensive therapeutic measures to induce a complete remission of RA. Thus, new onset amyloidosis usually warrants intensification of standard treatments for RA and/or the addition of newer experimental options (e.g., rituximab, tocilizumab, abatacept), several of which have shown the potential to ameliorate amyloidosis emerging in the context of RA.[97–99] One unusual feature of AA amyloid occurring in the context of RA is the finding in some cases of numerous cellular crescents, a feature that seems to auger a particularly dire outcome of the glomerular disease.[100,101] Finally, it is noteworthy that nonamyloidotic fibrillary glomerulonephritis has been reported as a rare association with RA.[102,103]

Renal Vasculitis

One of the more ominous late-stage complications of RA is the development of systemic (rheumatoid) vasculitis. The emergence of small- and/or medium-sized arteritis usually produces multisystem and visceral complications with their attendant high risks of morbidity and mortality. Renal vasculitis is a relatively rare component of rheumatoid vasculitis, but its development is associated with an ominous prognosis. Like secondary AA amyloidosis, patients with RA at risk for systemic vasculitis are those with protracted high levels of rheumatoid factor and persistently active disease, usually with cutaneous vasculitis and rheumatoid nodules occurring late in the course of joint destructive RA.

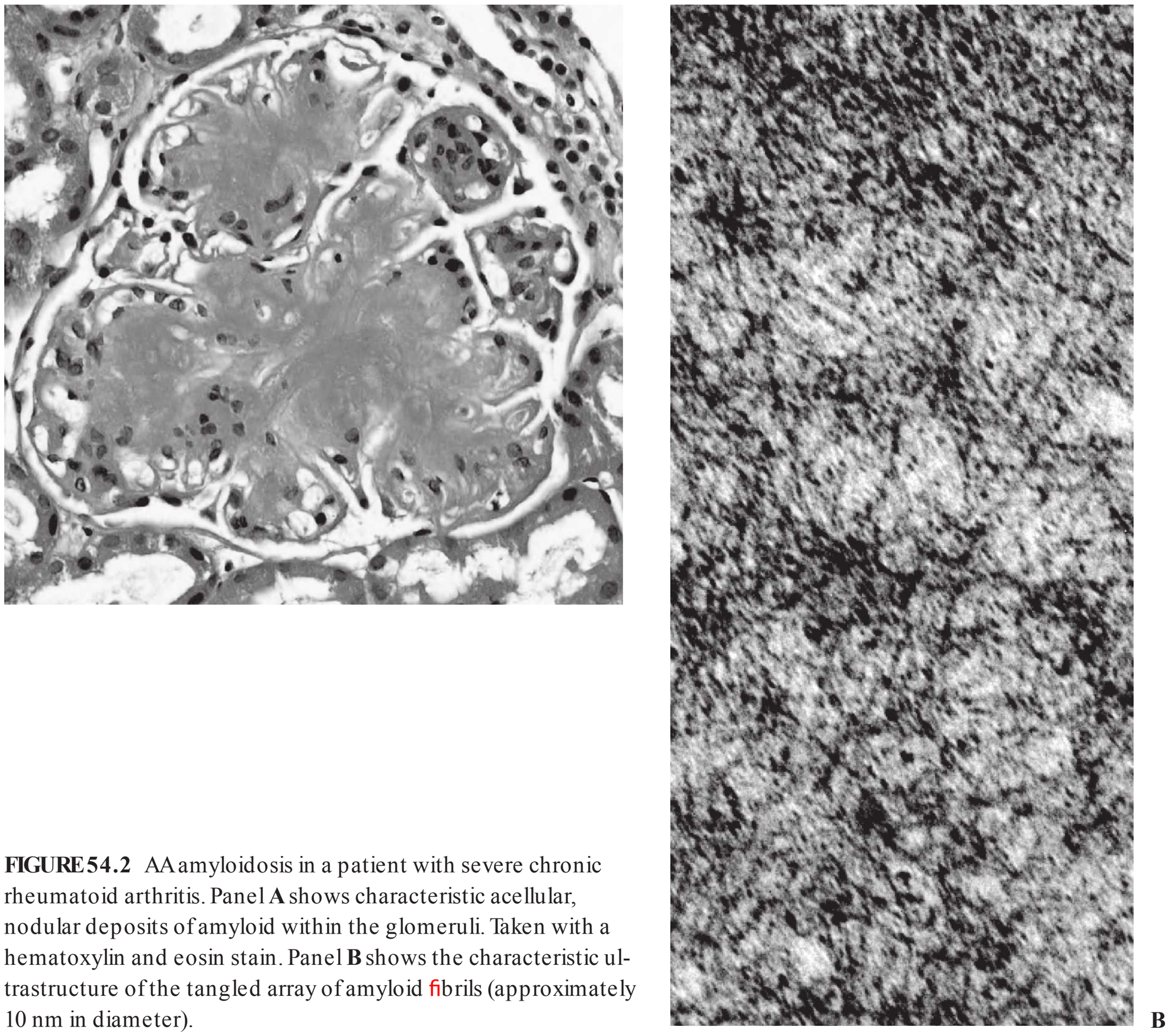


FIGURE 54.2 AA amyloidosis in a patient with severe chronic rheumatoid arthritis. Panel **A** shows characteristic acellular, nodular deposits of amyloid within the glomeruli. Taken with a hematoxylin and eosin stain. Panel **B** shows the characteristic ultrastructure of the tangled array of amyloid fibrils (approximately 10 nm in diameter).

Renal vasculitis is usually manifested by severe hypertension, nephritic syndrome, and often rapidly progressive renal failure.[104,105] ANCA, mostly antimyeloperoxidase autoantibodies, are usually (though not invariably) present.[106–108] Necrotizing, crescentic glomerulonephritis can be seen on a renal biopsy, as illustrated in Figure 54.3.[109] Aggressive therapy with high dose corticosteroids and cytotoxic drugs are indicated to counter the otherwise ominous prognosis of this form of renal vasculitis (see Chapter 48 on the treatment of vasculitis).

One perplexing aspect of the relationship between RA and systemic vasculitis is that anti-tumor necrosis factor (TNF) therapies have been recently recognized to have the potential to augment autoantibody production. This has been well documented for increments in titers of anti-dsDNA and flares of SLE and lupus nephritis.[110] Similar observations have been reported in patients with RA treated with anti-TNF therapies, which paradoxically appear to have precipitated the onset or flares of ANCA-associated renal vasculitis.[111–113] A detailed

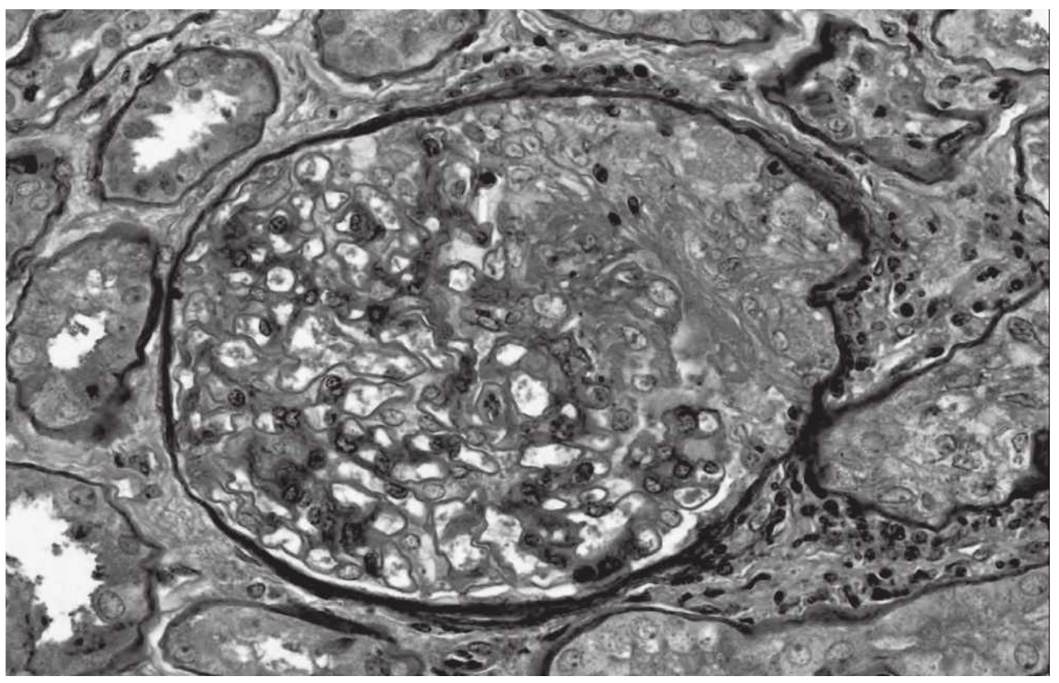


FIGURE 54.3 Antineutrophil cytoplasmic antibody (ANCA)–associated renal vasculitis in a patient with rheumatoid arthritis. A segmental necrotizing glomerulonephritis is present with fibrinoid necrosis, karyorrhexis, and a developing cellular crescent. Taken with a hematoxylin and eosin stain.

perspective on the role of anti-TNF therapies on autoantibody production and flares of autoimmune diseases remains a substantive challenge and the subject of ongoing research.

PRIMARY SJÖGREN SYNDROME

Sjögren syndrome is a relatively common autoimmune disease characterized by chronic inflammation and dysfunction of the exocrine glands. Lymphocytic infiltrates of salivary and lacrimal glands lead to typical clinical manifestations, including dry mouth, dry eyes, and parotid enlargement. The involvement of other exocrine glands can lead to dry skin, dryness of the upper respiratory tract, hypochlorhydria, pancreatic dysfunction, and vaginal dryness.[114,115] This autoimmune disorder can occur alone, as primary Sjögren syndrome, or in association with other autoimmune conditions, such as systemic lupus erythematosus, rheumatoid arthritis, and progressive systemic sclerosis (secondary Sjögren syndrome). This chapter will focus on renal abnormalities associated with primary Sjögren syndrome.

Similar to SLE, primary Sjögren syndrome predominantly affects women with a female to male ratio of 9:1. Although this condition is most frequently diagnosed in middle-aged individuals, children and elderly patients have been identified as well.[116–118] It may be difficult to recognize the diagnosis because the presenting signs and symptoms are typically nonspecific and mimic those seen in other conditions. In two large studies,[119,120] average delays of 4 and 6 years have been observed between the first symptom attributable to primary Sjögren syndrome and the diagnosis. This is of importance to the nephrologist who may encounter a patient with an unusual renal manifestation of primary Sjögren syndrome, before the underlying condition has been recognized.

Comparable to other autoimmune rheumatic disorders, the diagnosis of primary Sjögren syndrome requires the presence of a constellation of clinical, laboratory, and/or histologic features; the individual criteria are characteristic but not specifically diagnostic, because each can be attributed to alternative conditions. In 1993, a European Study Group published preliminary criteria for the classification of Sjögren syndrome to promote consistency in clinical studies of this condition.[121] In 2002, an American–European Consensus Group revised the rules to enhance the specificity of the criteria. Table 54.4 shows the widely accepted American–European classification criteria for Sjögren syndrome[122] published in 2002. The classification rules underscore the importance of the objective criteria (#3 to 6). The diagnosis of primary Sjögren syndrome can be based on the presence of three of four objective criteria or on the presence of any four of the six criteria as long as either the pathology or the autoantibody criteria (or both) are fulfilled. The diagnosis of secondary Sjögren syndrome requires symptoms of dry eyes and/or dry mouth (criteria #1 and/or 2) and any two items from the objective criteria #3, 4, or 5. The classification criteria exclude conditions and medications that may mimic features of Sjögren syndrome.

54.4 American–European Classification Criteria for Sjögren Syndrome

1.	**Ocular symptoms** – A positive response to at least one of three specific questions about dry eyes, sand, or gravel in the eyes or the use of tear substitutes >3 times a day
2.	**Oral symptoms** – A positive response to at least one of three specific questions about dry mouth for >3 months, swollen salivary glands as an adult, or drinking liquids to swallow dry foods.
3.	**Objective evidence of ocular involvement** – A positive Schirmer I test or positive Rose Bengal score (or other ocular dye score).
4.	**Histopathology** – A minor salivary gland biopsy that shows focal lymphocytic sialadenitis according to specific criteria.
5.	**Objective evidence of salivary gland involvement** – Specific abnormalities on at least one of the following tests: unstimulated whole salivary flow, parotid sialography, or salivary scintigraphy.
6.	**Autoantibodies** – Anti-SSA and/or anti-SSB[56]

SSA, Sjögren's syndrome-A; SSB, Sjögren's syndrome-B

It is important to emphasize that primary Sjögren syndrome is a systemic autoimmune condition that is frequently associated with constitutional symptoms and major organ dysfunction.[114,115,119,120,123] Constitutional symptoms commonly include fatigue and low-grade fever. Articular involvement is typically symmetric and nonerosive. Skin manifestations include Raynaud phenomenon, purpura, and vasculitis. Sensory neuropathies are the most common neurologic complications of primary Sjögren syndrome.[124,125] Patients may experience severe neuropathic pain before the systemic condition has been recognized. The lungs may be affected by a broad range of conditions including proximal and distal airway disease, interstitial pneumonitis, diffuse lymphoid hyperplasia of the lungs, and lymphoma.[126,127]

Approximately 4% of patients with Sjögren syndrome develop non-Hodgkin lymphoma.[115,128,129] Frequently, they are indolent mucosa-associated lymphoid tissue (MALT) lymphomas that predominantly involve the salivary glands; however, major organs including the kidneys, lungs, liver, and stomach may be affected as well. Less often, patients develop aggressive lymphomas that may arise de novo or from preexisting low-grade lymphomas. Skopouli and colleagues[120] found that among their patients with primary Sjögren syndrome, those with glomerulonephritis were at increased risk for lymphoma as well as peripheral neuropathy.

They observed that the development of glomerulonephritis and lymphoproliferative disorders was associated with purpura (especially palpable purpura), low levels of C4 complement, and mixed monoclonal cryoglobulinemia; they recommended vigilant monitoring of these patients.

Kidney Disorders in Patients with Primary Sjögren Syndrome

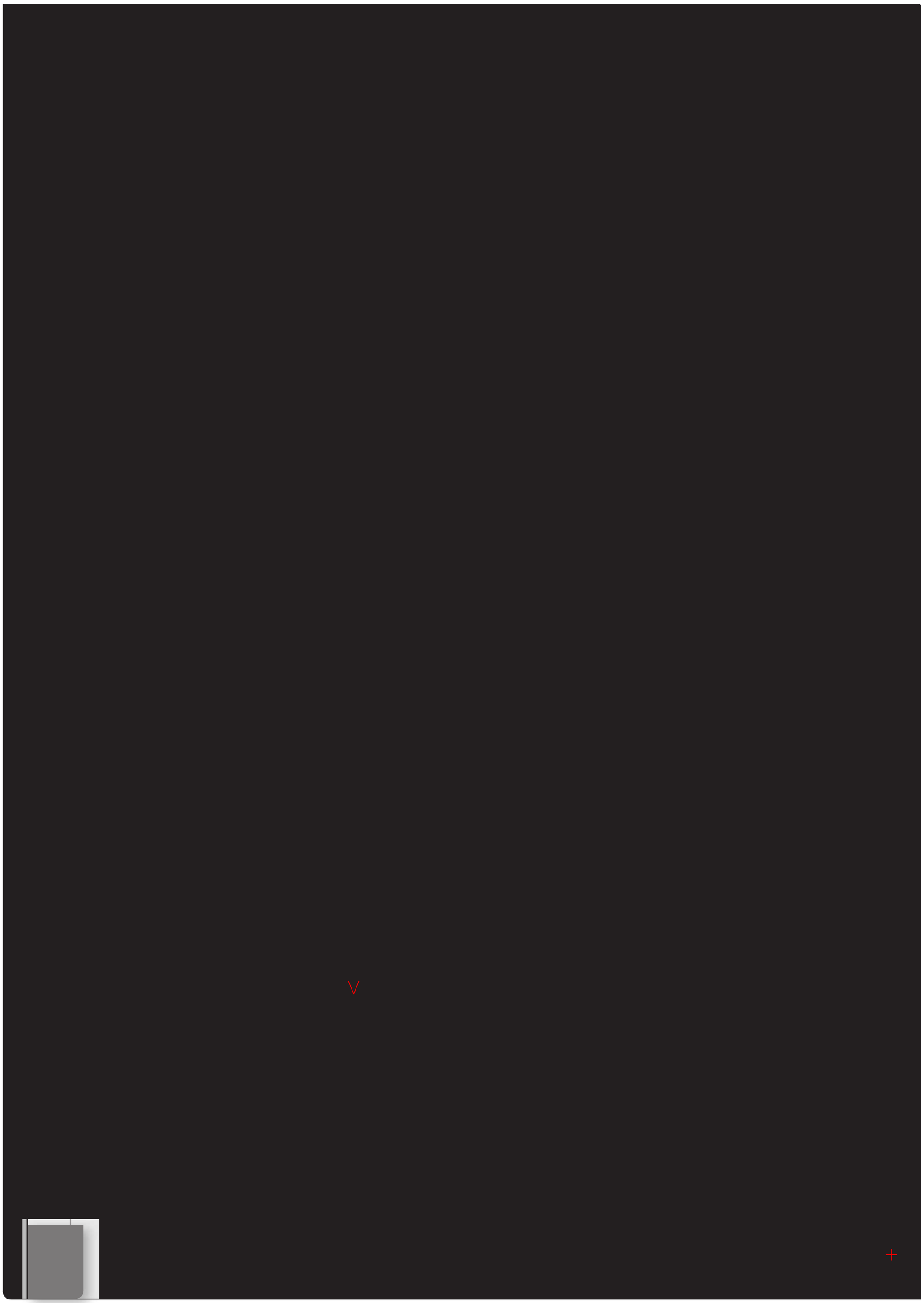
Table 54.5 shows the results of several relatively large, recently published studies that illustrate the broad range of kidney disorders that have been associated with primary Sjögren syndrome[119,130–135]. The patients fulfilled consensus criteria for the classification of primary Sjögren syndrome that were current at the time of the study—the European criteria[121] prior to 2002 and the American–European criteria,[122] subsequently. Goules et al.,[132] Ren et al.,[135] and Maripuri et al.[133] studied patients with primary Sjögren syndrome who were known to have kidney disease. Goules et al.[132] described 20 patients with overt kidney disease that the investigators felt called for a renal biopsy; 2 patients declined. Maripuri et al.[133] reported clinical and kidney pathology observations from 24 patients who had undergone a renal biopsy. Pertovaara et al.,[134] Aasarod et al.,[130] Bossini et al.,[131] and Lin et al.[119] sought to identify patients with renal involvement among cohorts of patients who had not been preselected for the presence of kidney disease. Pertovaara et al.,[134] Aasarod et al.,[130] and Bossini et al.[131] performed provocative tests to detect subclinical, latent kidney disorders that are frequently seen in patients with primary Sjögren syndrome; their studies included ammonium chloride loading tests to detect incomplete distal renal tubular acidosis (RTA) and water deprivation tests followed by the administration of I-deamino, 8-D arginine-vasopressin (DDAVP) to diagnose nephrogenic diabetes insipidus. It is unclear how often Lin and colleagues[119] used provocative tests to identify latent kidney disease in their patients. Overall, investigators have found that approximately a third of unselected patients with primary Sjögren syndrome have evidence of overt or latent renal involvement. A small fraction of those typically have overt kidney disease, which has a substantial impact on the patient's health. For example, Bossini et al.[131] found that 16 of 60 patients (27%) had laboratory abnormalities consistent with tubular and/or glomerular dysfunction. Only 4 presented with overt manifestations of kidney disease—2 patients had nephrotic syndrome, 1 had hypokalemic quadriparesis, and 1 had recurrent renal calculi and nephrocalcinosis associated with complete distal RTA.

Distal Renal Tubular Acidosis

Distal RTA (often incomplete distal RTA) has been reported in approximately 10% to 70% of patients with primary Sjögren syndrome.[119,130,132,134–142] Particularly high incidence rates are seen in cohorts that include substantial numbers of Sjögren patients with previously recognized kidney disease and/or a history of urolithiasis.[132,135,136] Patients with complete or incomplete distal RTA are at increased risk for nephrolithiasis or nephrocalcinosis. Hypocitraturia has been observed frequently among these patients[130,136] and increases the risk of forming calcium stones. Screening for hypocitraturia may be useful when evaluating patients with primary Sjögren syndrome, because this may facilitate the recognition of complete or incomplete distal RTA and may underscore the need for citrate supplementation to decrease the risk of nephrolithiasis, nephrocalcinosis, and bone disease observed in these patients.

Several investigators have sought to identify other clinical features that predict the occurrence of distal RTA among patients with primary Sjögren syndrome. Pertovaara and colleagues[134] found by multivariate logistic regression analysis that hypertension, proteinuria ($<$0.5 g per day in all) and the duration of xerostomia were each independently associated with the occurrence of distal RTA among their patients with primary Sjögren syndrome. On the other hand, Ren and colleagues[135] found that their Sjögren patients with RTA were significantly younger and were significantly more likely to have hypergammaglobulinemia than those without RTA. An association of hypergammaglobulinemia with distal RTA has been noted in some,[143,144] but not all[137,140] studies of Sjögren syndrome. The occurrence of several autoantibodies commonly detected in patients with primary Sjögren syndrome (antinuclear antibody [ANA], anti-Sjögren's syndrome-A [SSA], and anti-Sjögren's syndrome-B [SSB]) has not been consistently linked with the presence of distal RTA.[130,134,135,137,140] Furthermore, increased urinary excretion of β-2 microglobulin, N-acetyl-β-amino-glucosidase (NAG), or retinol binding protein (RBP) has been observed among patients with distal RTA in some,[130] but not all[135] recent studies of primary Sjögren syndrome. Thus, it appears that hypergammaglobulinemia, serum levels of ANA, anti-SSA, and anti-SSB autoantibodies, as well as the urinary excretion rate of β-2 microglobulin, NAG, or RBP are not reliable predictors of the occurrence of distal RTA in patients with primary Sjögren syndrome.

Clinical and pathologic studies offer insights into the pathogenesis of distal RTA in patients with primary Sjögren syndrome. Patients have been diagnosed functionally to have secretory defect distal RTA, based on a failure to acidify urine (spontaneously or after the administration of ammonium chloride or furosemide), a positive urinary anion gap despite systemic acidosis (suggesting impaired urinary ammonium excretion), normal or low serum potassium values, and an abnormally low urine–blood pCO_2 difference during a bicarbonate infusion.[145–148] Apical H^+-ATPase and basolateral anion exchanger 1 (AE1) mediate H^+ secretion from α-intercalated cells in the collecting ducts. Several studies of primary Sjögren patients with distal RTA have shown little or no immunoreactive H^+-ATPase in collecting duct cells despite the presence of normal appearing α-intercalated cells by light and electron microscopy.[145–151] Absent AE1 immunoreactivity has been observed in some of these patients as well.[146,148,150,151] Pathogenic mechanisms underlying the absence of H^+-ATPase and AE1 have not been fully elucidated. For example, it is unclear to what degree cellular and/



or autoantibody-mediated mechanisms are involved. A cell-mediated inflammatory process could disrupt key transporters in α-intercalated cells, but several investigators have pointed out that inflammatory tubulointerstitial infiltrates have not been seen consistently in Sjögren patients with distal RTA.[140,148] This could represent a kidney biopsy sampling artifact, or humoral mechanisms may be involved. Autoantibodies directed against α-intercalated cells have been detected in a Sjögren patient with secretory defect distal RTA.[147]

Furthermore, Takemoto and colleagues[152,153] have recently shown that high titers of autoantibody against carbonic-anhydrase-II may contribute to the pathogenesis of RTA in primary Sjögren syndrome. Carbonic anhydrase II is found in proximal and distal renal tubular epithelial cells where it plays an important role in the bicarbonate reabsorption and regeneration. Takemoto and colleagues[152] found significantly higher serum anti–carbonic-anhydrase-II levels in 13 patients with primary Sjögren syndrome diagnosed with distal RTA (that was confirmed by the ammonium chloride loading test in 7), compared to 33 Sjögren patients without RTA and 19 normal controls. By multivariate logistic regression analysis, anti–carbonic-anhydrase-II antibody levels and the duration of disease were each independently associated with the presence of RTA. This group of investigators has also shown that mice immunized to produce high titers of anti–carbonic-anhydrase-II antibody develop a urinary acidification defect that is consistent with incomplete distal RTA.[153] These observations raise the interesting possibility that autoantibodies to H^+-ATPase, AE1, and/or carbonic-anhydrase-II may contribute to RTA observed in these patients.

Proximal Renal Tubular Acidosis and Fanconi Syndrome

As illustrated in Table 54.5, proximal RTA and Fanconi syndrome are reported much less often among patients with primary Sjögren syndrome compared to distal RTA. It is interesting to speculate whether autoantibodies against anti–carbonic-anhydrase-II or membrane proteins, such as β-fodrin,[154] as well as cell-mediated injury, might contribute to the development of proximal RTA and Fanconi syndrome in these patients. Recent reviews have identified approximately a dozen case reports of primary Sjögren syndrome with features of proximal tubular dysfunction consistent with Fanconi syndrome and proximal RTA (in most).[155,156] Of note, many of these patients also manifested abnormalities in distal tubular function, compatible with distal RTA and/or nephrogenic diabetes insipidus. Phosphaturia was observed frequently among these cases and in other series of patients with Sjögren syndrome,[136,138] and may contribute to the development of osteomalacia, which is seen in some patients with primary Sjögren syndrome.[157,158] Supportive treatment for Fanconi syndrome includes supplements to correct metabolic acidosis, hypokalemia, and hypophosphatemia. Five of the 10 patients reviewed by Wang et al.[156] were also treated with Immunosuppressants (low-to-intermediate dose prednisolone in 4 patients and mycophenolate mofetil [1g per day] in 1 patient). Although many of these patients showed signs of improved tubular (and glomerular) function following immunosuppression, no studies have compared the value of immunosuppression to supportive therapy. Furthermore, it is important to weigh the risks of immunosuppression, including the risk that corticosteroids may aggravate the bone disease that may occur in Sjögren patients with renal tubular acidosis and Fanconi syndrome.[157,158]

Hypokalemic Paralysis

Patients with primary Sjögren syndrome are at risk for developing hypokalemia as a complication of immune-mediated interstitial nephritis and RTA.[159] It is noteworthy that a substantial number of these patients have presented with severe hypokalemia complicated by paralysis, respiratory failure, and/or cardiac arrest.[135,160,161] For example, in Ren et al.'s[135] study of 130 Sjögren patients with previously recognized renal involvement, 61 (47%) had hypokalemia and 9 consulted a nephrologist because of hypokalemic paralysis; 1 died following a cardiac arrest. Soy and colleagues[161] identified 18 cases of hypokalemic periodic paralysis associated with Sjögren syndrome in a Medline search of the literature between 1966 and 2004; 3 experienced respiratory arrest. Seven patients, including the 3 who experienced respiratory arrest, were treated with glucocorticoids. Although electrolyte and alkali replacement therapy was successful in many patients, corticosteroids (occasionally in combination with another immunosuppressant) have been recommended for patients with severe, persistent, or recurring manifestations of profound hypokalemia.[160,161]

Bartter Syndrome and Gitelman Syndrome

Small numbers of Sjögren patients have been described who have these rare tubular disorders.[162–167] In two cases, sequencing of the Na^+/Cl^- cotransporter (NCCT) gene showed that Gitelman syndrome was acquired, not inherited.[163,165] In the kidney biopsy sample of one of those patients, NCCT could not be detected in the distal convoluted tubules by immunohistochemical staining.[165] Incubation of that patient's serum with a normal mouse kidney showed a pattern of reactivity, which suggested that she had developed circulating autoantibodies to NCCT.[165]

Nephrogenic Diabetes Insipidus

Aasarod et al.[130] and Bossini et al.[131] studied cohorts of patients with primary Sjögren syndrome who were not specifically selected because they were previously known to have kidney disease. Each found that about 20% of their Sjögren patients had urinary concentrating abnormalities consistent with nephrogenic diabetes insipidus. In many of these cases, the urine was concentrated after water deprivation and the administration of DDAVP, but urine osmolality failed to reach normal maximum age-adjusted values. Consequently, for these patients, the urine concentrating defect was mild

and asymptomatic. Other patients with primary Sjögren syndrome may experience symptomatic nephrogenic diabetes insipidus due to immune-mediate tubular dysfunction or protracted profound hypokalemia. Alternatively, Sjögren patients may induce polyuria by drinking large volumes of fluids to quench their symptoms associated with xerostomia.

Kidney Biopsy Findings

Maripuri and colleagues[133] described the clinical data and the renal pathology of 24 patients with primary Sjögren syndrome who underwent a kidney biopsy at the Mayo Clinic from 1967 to 2007. The predominant lesion was acute or chronic tubulointerstitial nephritis (TIN) in 17 patients (71%) as illustrated in Figure 54.4. Eleven of these patients had chronic TIN, making that the most common kidney biopsy diagnosis. Acute TIN with tubulitis was seen in 6 patients, 4 of whom had RTA. Diverse glomerular lesions were the predominant histologic change in 7 patients. Two had cryoglobulinemic membranoproliferative glomerulonephritis (MPGN); 2 had focal segmental glomerulosclerosis (FSGS), 1 had membranous glomerulonephritis (MGN), 1 had minimal change, and 1 had global glomerulosclerosis. Finally, 1 had chronic TIN and FSGS.

Goules et al.[132] found TIN in 10 patients, MPGN in 5, and mesangial proliferative GN in 4. The tubulointerstitial infiltrates included lymphocytes, plasma cells, and monocytes. The lymphocytes were predominantly CD4+, comparable to those seen in Sjögren salivary gland infiltrates. Many of the patients in the study with GN had mixed monoclonal cryoglobulinemia IgM kappa (IgMκ) and low levels of C4 complement. Two patients with glomerular disease, but none of their patients with isolated TIN, developed end-stage renal failure.

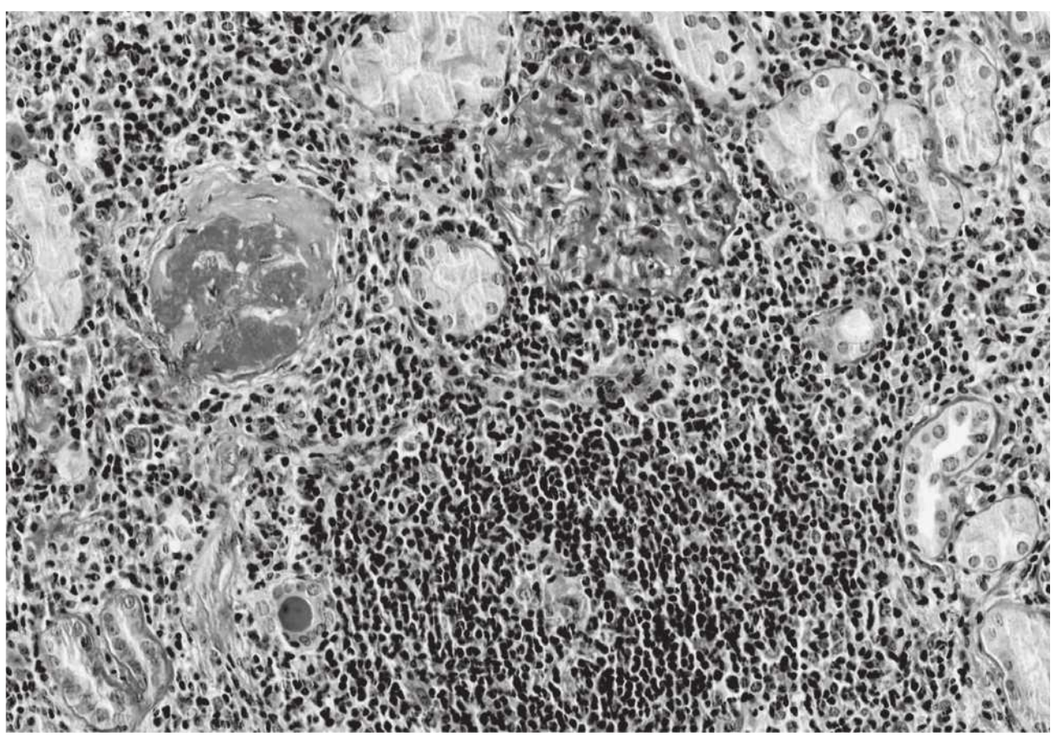


FIGURE 54.4 Severe chronic interstitial nephritis in a patient with Sjögren syndrome. The mononuclear lymphoid cells have infiltrated the interstitium causing extensive tubular atrophy; an obsolescent glomerulus is present indicating the associated nephron damage, but the other viable glomerulus shows no evidence of substantive pathology. Taken using a periodic acid Schiff stain.

Other relatively large studies of kidney biopsies in patients with primary Sjögren syndrome have also shown a diverse range of glomerular lesions, including mesangial proliferative GN, MGN, FSGS, and diffuse or focal proliferative GN.[119,135] The range of glomerular disease possibly associated with primary Sjögren syndrome has been expanded further by case reports of ANCA-positive necrotizing crescentic GN, immunoglobulin A (IgA) nephropathy, amyloidosis, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura.[168–173] However, the causal relationship of these glomerular lesions with primary Sjögren syndrome is unknown.

Treatment

Ren and colleagues[135] noted that 96 of their 130 primary Sjögren patients with clinically evident renal involvement were treated with immunosuppressants. Approximately two thirds of those treated received corticosteroids alone; the others received an additional immunosuppressive agent, frequently oral or intravenous cyclophosphamide. Although detailed information about the clinical and histologic characteristics of the patients treated with these regimens was not provided, they do specify that renal function improved or normalized following treatment in 25 of 35 patients with an elevated serum creatinine. Four patients progressed to end-stage renal failure, and 4 died (2 from infection, 1 from a cerebrovascular accident, and 1 from lymphoma). They concluded that immunosuppressive therapy may be beneficial for some patients with primary Sjögren syndrome, especially those with major organ system involvement.

Maripuri et al.[133] reported that 20 of their 24 patients were treated with prednisone, often alone and occasionally with cyclophosphamide, mycophenolate mofetil, rituximab, or plasma exchange (for cryoglobulinemia). Immunosuppression was associated with statistically significant improvements in estimated glomerular filtration rate and proteinuria among 17 patients who had more than 3 months of follow-up. Consequently, the authors recommended a course of corticosteroids as first-line therapy for all primary Sjögren patients with active glomerular and/or tubulointerstitial disease. Because this and other studies have not been designed to determine which immunosuppressive regimen has the most favorable risk/benefit ratio, the authors suggested that further immunosuppressive treatments need to be individualized based on clinical and pathology observations as well as the impact of the initial treatment regimen.

Goules et al.[132] indicated that most patients with primary Sjögren syndrome followed at the universities of Ioannina and Athens, Greece were treated according to a somewhat different strategy. Goules and colleagues noted that 9 of 10 patients with glomerular disease (confirmed by kidney biopsy in all but 1) received immunosuppression with methylprednisolone alone in 2 cases, methylprednisolone and azathioprine in 1 case, and methylprednisolone and cyclophosphamide in 6 cases. On the other hand, only 3 of 10 patients with TIN

received immunosuppression. The authors have observed that the clinical course of TIN in their primary Sjögren patients has been relatively favorable and suggest that kidney biopsy and immunosuppression may not be necessary for many of those patients. On the other hand, they are concerned that the prognosis of primary Sjögren patients with glomerular disease is less favorable. Consequently, kidney biopsy assessment and immunosuppressive treatments should be considered for many of these patients.

POLYMYOSITIS AND DERMATOMYOSITIS

Polymyositis (PM) and dermatomyositis (DM) are part of a heterogeneous group of rare inflammatory myopathies, characterized by muscle weakness and inflammation.[174–177] Among patients with DM and PM, the female to male ratio is approximately 2:1.[178] DM can occur at any age, but PM is rarely seen in children. Muscle biopsies show evidence of autoimmune pathogenesis, mediated predominantly by cytotoxic T lymphocytes in PM and complement-associated microangiopathy in DM. Although DM and PM are often idiopathic conditions, they may be seen in association with various cancers or other autoimmune conditions.[179] Patients with PM and DM typically present with symmetric proximal muscle weakness that evolves over several weeks to months and causes difficulty with a range of activities including climbing stairs, getting out of a chair, and performing tasks overhead. Distal muscles may be affected late in the course of the disease. In contrast to myasthenia, extraocular muscles are spared. Sensation is normal, and deep tendon reflexes are intact unless the relevant muscles are extremely weak.

Recognition of DM is often facilitated by characteristic cutaneous manifestations that are typically seen before or coincident with the development of muscle weakness. The heliotrope rash (a purplish discoloration of the eyelids) and Gottron papules (a scaly erythematous eruption on the extensor surfaces of the hands and fingers) are considered pathognomonic for DM.[177] Lacking a pathognomonic clinical sign, the diagnosis of PM may be more difficult. Muscle biopsy is needed to establish a definitive diagnosis of DM or PM and to rule out conditions that mimic myositis, including a broad range of muscular dystrophies, metabolic diseases, mitochondrial disorders, and neurologic diseases.[174] Infectious, endocrine, and drug-induced etiologies must be considered as well.

PM and DM are systemic autoimmune conditions that often affect extramuscular systems including the lungs, heart, and gastrointestinal tract, as well as the skin and joints. Pulmonary manifestations (including interstitial lung disease, respiratory muscle weakness, and aspiration pneumonia) are common causes of morbidity and mortality among patients with PM and DM.[180,181] Antibodies against amino-tRNA-synthetases (e.g., anti-Jo-1) are strongly associated with interstitial lung disease, as well as fever, arthritis, characteristic hyperkeratotic lesions along the fingers called mechanic's hands, and Raynaud phenomenon; this constellation constitutes antisynthetase syndrome.[174,177] Cardiac involvement may cause conduction abnormalities, arrhythmias, or congestive heart failure in some cases. Gastrointestinal manifestations include dysphagia, aspiration, delayed gastric emptying, and rarely, intestinal vasculitis. Joint involvement typically leads to nondeforming symmetric arthritis.

Kidney Disorders in Patients with Polymyositis and Dermatomyositis

In general, two types of renal involvement have been described among patients with DM or PM. If severe, myositis may cause myoglobinemia, myoglobinuria, and acute kidney injury.[182–184] Furthermore, various glomerular diseases have been reported, though rarely (particularly, mesangial proliferative GN in PM and membranous nephropathy as well as mesangial proliferative GN in DM).[184–189] The presence of glomerular disease in patients with DM and PM should prompt careful, serial evaluations to rule out the concurrence of another collagen vascular disease or a malignancy that may underlie the development of glomerulopathy in these patients.

It is difficult to describe the scope and frequency of renal involvement in patients with DM and PM because there are very few studies that have examined renal parameters in a cohort of myositis patients who were not selected for the presence of kidney disease. A recent study of 65 Taiwanese patients with DM or PM (admitted to the Chang Gung Memorial Hospital in Taipei, Taiwan between 1992 and 2002) provides an interesting perspective.[184] Yen and colleagues[184] found that 14 of 65 patients (22%) had evidence of renal involvement. Five of these patients had PM; 1 had moderate proteinuria and was considered to have SLE as well. Four PM patients died suddenly because of severe hyperkalemia due to rhabdomyolysis and myoglobinuric acute renal failure. Of the 9 DM patients with renal involvement, 3 had a concurrent autoimmune condition (SLE +/or rheumatoid arthritis), and 1 had cancer. Five DM patients developed myoglobinuric acute renal failure; 4 required hemodialysis.

Myoglobinuric Acute Renal Failure

Overall, Yen and colleagues[184] observed acute tubular necrosis due to rhabdomyolysis in 9 of their 65 patients (14%) with DM or PM; 4 died suddenly because of hyperkalemia and metabolic acidosis. The incidence of these adverse events was surprisingly high and underscores the importance of careful monitoring and preventive measures. Several clinical features may increase the risk of these complications, including an unusually acute presentation of myositis, a poor response to immunosuppressive therapy, and comorbid conditions that impair renal perfusion and the clearance of myoglobin. Treatment typically includes immunosuppression to quell immune-mediated muscle injury and hydration to optimize renal blood flow and maintain a dilute diuresis. Alkalinization of the urine to inhibit pigment cast formation should be considered as well. Hemodialysis may be required

to manage acute renal failure, hyperkalemia, hyperphosphatemia, and/or metabolic acidosis if standard medical interventions are not effective.

Glomerular Disease

Several reviews of the literature have found very small numbers of patients with DM or PM who had glomerular disease without evidence of an associated systemic autoimmune condition or a malignancy.[185–188] There are case reports of approximately a dozen patients with PM who had mesangial proliferative glomerulonephritis and about a half dozen patients with DM who had membranous nephropathy. Smaller numbers of patients with PM were noted to have membranous nephropathy, crescentic glomerulonephritis, or focal glomerulosclerosis. A few patients with DM were reported to have mesangial proliferative glomerulonephritis, diffuse proliferative glomerulonephritis, or IgA nephropathy.

Given the small number of patients with DM or PM who have developed glomerular disease, it is important to look for a concurrent systemic autoimmune disease, such as SLE, Sjögren syndrome, vasculitis, rheumatoid arthritis, systemic sclerosis, and MCTD. Patients with MCTD typically have anti-U1 ribonucleoprotein (RNP) antibodies and overlapping features of SLE, PM, and systemic sclerosis, but this constellation of characteristic findings may evolve slowly over several years before the diagnosis is evident. Renal involvement has been described in 10% to 50% of MCTD patients. Membranous nephropathy has been the most common glomerular lesion, but mesangial proliferative GN, MPGN, SRC, vasculitis, and collapsing glomerulopathy have been reported as well.[190,191]

A number of studies have shown that patients with DM and PM are at an increased risk for a broad range of malignancies.[192] Buchbinder and colleagues[193] studied the risk of cancer in a large cohort of patients with biopsy-proven DM or PM; they found a sixfold increased risk among patients with DM and a twofold increased risk among those with PM compared to the general population after adjusting for age and gender. The risk of malignancy gradually declined over 5 years after the diagnosis of myositis, but remained statistically elevated for colorectal and pancreatic cancer beyond more than 5 years of follow-up among patients with DM in a pooled analysis of three large Scandinavian studies.[194] These observations underscore the diagnostic challenge presented by patients with DM or PM, who may also have one of the glomerular diseases that have been associated with an increased risk of malignancy. Several cancer-screening strategies have been proposed, but additional studies are needed to refine our approach to the evaluation of these patients.[174,195]

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REFERENCES

1. LeRoy EC, Black C, Fleischmajer R et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202–205. http://www.ncbi.nlm.nih.gov/pubmed/3361530
2. Walker JG, Ahern MJ, Smith MD, et al. Scleroderma renal crisis: poor outcome despite aggressive antihypertensive treatment. Intern Med J. 2003;33(5–6):216–220.
3. Chiff ot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum. 2008;37(4):223–235.
4. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev. 2010;9(5):A311–A318.
5. Granel B, Bernard F, Chevillard C. Genetic susceptibility to systemic sclerosis from clinical aspect to genetic factor analyses. Eur J Intern Med. 2009;20(3):242–252.
6. Radic M, Martinovic KD, Radic J. Infectious disease as aetiological factor in the pathogenesis of systemic sclerosis. Neth J Med. 2010;68(11):348–353. http://www.ncbi.nlm.nih.gov/pubmed/21158008
7. Romano E, Manetti M, Guiducci S, et al. The genetics of systemic sclerosis: an update. Clin Exp Rheumatol. 2011;29(2 Suppl 65):S75–S86.
8. Hunzelmann N, Krieg T. Scleroderma: from pathophysiology to novel therapeutic approaches. Exp Dermatol. 2010;19(5):393–400.
9. Katsumoto TR, Whitfield ML, Connolly MK. The pathogenesis of systemic sclerosis. Annu Rev Pathol. 2011;6:509–537. http://www.ncbi.nlm.nih.gov/pubmed/21090968
10. Manetti M, Guiducci S, Ibba-Manneschi L, Matucci-Cerinic M. Mechanisms in the loss of capillaries in systemic sclerosis: angiogenesis versus vasculo- genesis. J Cell Mol Med. 2010;14(6A):1241–1254.
11. Yamamoto T. Scleroderma—pathophysiology. Eur J Dermatol. 2009;19(1):14–24. http://www.ncbi.nlm.nih.gov/pubmed/19059831
12. Kahaleh MB, LeRoy EC. Autoimmunity and vascular involvement in systemic sclerosis (SSc). Autoimmunity. 1999;31(3):195–214. http://www.ncbi.nlm.nih.gov/pubmed/10739336
13. Fleming JN, Schwartz SM. The pathology of scleroderma vascular disease. Rheum Dis Clin North Am. 2008;34(1):41–55. http://www.ncbi.nlm.nih.gov/pubmed/18329531
14. Distler JH, Jungel A, Pileckyte M, et al. Hypoxia-induced increase in the production of extracellular matrix proteins in systemic sclerosis. Arthritis Rheum. 2007;56(12):4203–4215. http://www.ncbi.nlm.nih.gov/pubmed/18050252
15. Higgins DF, Kimura K, Bernhardt WM, et al. Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition. J Clin Invest. 2007;117(12):3810–3820.
16. Bosello S, De LG, Tolusso B, et al. B cells in systemic sclerosis: a possible target for therapy. Autoimmun Rev. 2011;10(10):624–630. http://www.ncbi.nlm.nih.gov/pubmed/21545850
17. Baroni SS, Santillo M, Bevilacqua F, et al. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med. 2006;354(25):2667–2676. http://www.ncbi.nlm.nih.gov/pubmed/16790699
18. Penn H, Howie AJ, Kingdon EJ, et al. Scleroderma renal crisis: patient characteristics and long-term outcomes. QJM. 2007;100(8):485–494. http://www.ncbi.nlm.nih.gov/pubmed/17601770
19. Haviv YS, Safadi R. Normotensive scleroderma renal crisis: case report and review of the literature. Ren Fail. 1998;20(5):733–736. http://www.ncbi.nlm.nih.gov/pubmed/9768442
20. Helfrich DJ, Banner B, Steen VD, Medsger TA Jr. Normotensive renal failure in systemic sclerosis. Arthritis Rheum. 1989;32(9):1128–1134. http://www.ncbi.nlm.nih.gov/pubmed/2775321
21. Teixeira L, Mouthon L, Mahr A, et al. Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. Ann Rheum Dis. 2008;67(1):110–116. http://www.ncbi.nlm.nih.gov/pubmed/17557890
22. Steen VD. Scleroderma renal crisis. Rheum Dis Clin North Am. 2003;29(2):315–333. http://www.ncbi.nlm.nih.gov/pubmed/12841297
23. Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum. 1998;41(9):1613–1619. http://www.ncbi.nlm.nih.gov/pubmed/9751093
24. Tormey VJ, Bunn CC, Denton CP, Black CM. Anti-fibrillarin antibodies in systemic sclerosis. Rheumatology (Oxford). 2001;40(10):1157–1162. http://www.ncbi.nlm.nih.gov/pubmed/11600746

25. Gavras H, Gavras I, Cannon PJ, Brunner HR, Laragh JH. Is elevated plasma renin activity of prognostic importance in progressive systemic sclerosis? Arch Intern Med. 1977;137(11):1554–1558.
http://www.ncbi.nlm.nih.gov/pubmed/921442

26. Steen VD, Medsger TA Jr, Osial TA Jr, et al. Factors predicting development of renal involvement in progressive systemic sclerosis. Am J Med. 1984; 76(5): 779–786.

27. Clements PJ, Lachenbruch PA, Furst DE, et al. Abnormalities of renal phys-iology in systemic sclerosis. A prospective study with 10-year followup. Arthritis Rheum. 1994;37(1):67–74.

28. Fleischmajer R, Gould AB. Serum renin and renin substrate levels in scleroderma. Proc Soc Exp Biol Med. 1975;150(2):374–379.
http://www.ncbi.nlm.nih.gov/pubmed/1208551

29. Kadono T, Kikuchi K, Sato S, et al. Elevated plasma endothelin levels in systemic sclerosis. Arch Dermatol Res. 1995;287(5):439–442.
http://www.ncbi.nlm.nih.gov/pubmed/7625853

30. Kobayashi H, Nishimaki T, Kaise S, et al. Immunohistological study endothelin-1 and endothelin-A and B receptors in two patients with scleroderma renal crisis. Clin Rheumatol. 1999;18(5):425–427.
http://www.ncbi.nlm.nih.gov/pubmed/10524561

31. Mouthon L, Mehrenberger M, Teixeira L, et al. Endothelin-1 expression in scleroderma renal crisis. Hum Pathol. 2011;42(1):95–102.
http://www.ncbi.nlm.nih.gov/pubmed/20971496

32. Batal I, Domsic RT, Medsger TA, Bastacky S. Scleroderma renal crisis: a pathology perspective. Int J Rheumatol. 2010;2010:543704.
http://www.ncbi.nlm.nih.gov/pubmed/20981312

33. Donohoe JF. Scleroderma and the kidney. Kidney Int. 1992;41(2):462–477.
http://www.ncbi.nlm.nih.gov/pubmed/1552721

34. Caskey FJ, Thacker EJ, Johnston PA, Barnes JN. Failure of losartan to control blood pressure in scleroderma renal crisis. Lancet. 1997;349(9052):620.
http://www.ncbi.nlm.nih.gov/pubmed/9057740

35. Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. Ann Intern Med. 2000;133(8):600–603.
http://www.ncbi.nlm.nih.gov/pubmed/11033587

36. Denton CP, Black CM. Scleroderma—clinical and pathological advances. Best Pract Res Clin Rheumatol. 2004;18(3):271–290.

37. Scorza R, Rivolta R, Mascagni B, et al. Effect of iloprost infusion on the resistance index of renal vessels of patients with systemic sclerosis. J Rheumatol. 1997;24(10):1944–1948.

38. Shor R, Halabe A. New trends in the treatment of scleroderma renal crisis. Nephron. 2002;92(3):716–718.
http://www.ncbi.nlm.nih.gov/pubmed/12372964

38a. 2009 Abstracts of the American College of Rheumatology, Annual Scientif c Meeting, October 16–21, 2009, Philadelphia, PA. Arthritis & Rheumatism, 60:1. Suppl 10:451.
http://www.ncbi.nlm.nih.gov/pubmed/22953151

39. Steen VD, Costantino JP, Shapiro AP, Medsger TA Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Intern Med. 1990;113(5):352–357.

40. Tsakiris D, Simpson HK, Jones EH, et al. Report on management of renal failure in Europe, XXVI, 1995. Rare diseases in renal replacement therapy in the ERA-EDTA Registry. Nephrol Dial Transplant. 1996;11(Suppl 7):4–20.

41. Bleyer AJ, Tell GS, Evans GW, Ettinger WH Jr, Burkart JM. Survival of patients undergoing renal replacement therapy in one center with special emphasis on racial differences. Am J Kidney Dis. 1996;28(1):72–81.
http://www.ncbi.nlm.nih.gov/pubmed/8712225

42. Pham PT, Pham PC, Danovitch GM, et al. Predictors and risk factors for recurrent scleroderma renal crisis in the kidney allograft: case report and review of the literature. Am J Transplant. 2005;5(10):2565–2569.
http://www.ncbi.nlm.nih.gov/pubmed/16162209

43. Anders HJ, Wiebecke B, Haedecke C, et al. MPO-ANCA-Positive crescentic glomerulonephritis: a distinct entity of scleroderma renal disease? Am J Kidney Dis. 1999;33(4):e3.

44. Arad U, Balbir-Gurman A, Doenyas-Barak K, et al. Anti-neutrophil antibody associated vasculitis in systemic sclerosis. Semin Arthritis Rheum. 2011 [Epub ahead of print].

45. Arnaud L, Huart A, Plaisier E, et al. ANCA-related crescentic glomerulonephritis in systemic sclerosis: revisiting the "normotensive scleroderma renal crisis". Clin Nephrol. 2007;68(3):165–170.
http://www.ncbi.nlm.nih.gov/pubmed/18184529

46. Endo H, Hosono T, Kondo H. Antineutrophil cytoplasmic autoantibodies in 6 patients with renal failure and systemic sclerosis. J Rheumatol. 1994;21(5):864–870.
http://www.ncbi.nlm.nih.gov/pubmed/8064727

47. Katrib A, Sturgess A, Bertouch JV. Systemic sclerosis and antineutrophil cyto-plasmic autoantibody-associated renal failure. Rheumatol Int. 1999;19(1–2): 61–63.
http://www.ncbi.nlm.nih.gov/pubmed/10651085

48. Tomioka M, Hinoshita F, Miyauchi N, et al. ANCA-related crescentic glomerulonephritis in a patient with scleroderma without marked dermatological change and malignant hypertension. Intern Med. 2004;43(6):496–502.
http://www.ncbi.nlm.nih.gov/pubmed/15283187

49. Ruffatti A, Sinico RA, Radice A, et al. Autoantibodies to proteinase 3 and myeloperoxidase in systemic sclerosis. J Rheumatol. 2002;29(5):918–923.
http://www.ncbi.nlm.nih.gov/pubmed/12022350

50. Akimoto S, Ishikawa O, Tamura T, Miyachi Y. Antineutrophil cytoplasmic au-toantibodies in patients with systemic sclerosis. Br J Dermatol. 1996;134(3): 407–410.

51. Locke IC, Worrall JG, Leaker B, Black CM, Cambridge G. Autoantibodies to myeloperoxidase in systemic sclerosis. J Rheumatol. 1997;24(1):86–89.
http://www.ncbi.nlm.nih.gov/pubmed/9002016

52. D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of f fty-eight autopsy cases and f fty-eight matched controls. Am J Med. 1969;46(3):428–440.
http://www.ncbi.nlm.nih.gov/pubmed/5780367

53. Kingdon EJ, Knight CJ, Dustan K, et al. Calculated glomerular f ltration rate is a useful screening tool to identify scleroderma patients with renal impairment. Rheumatology (Oxford). 2003;42(1):26–33.

54. Livi R, Teghini L, Pignone A, et al. Renal functional reserve is impaired in patients with systemic sclerosis without clinical signs of kidney involvement. Ann Rheum Dis. 2002;61(8):682–686.

55. Mohamed RH, Zayed HS, Amin A. Renal disease in systemic sclerosis with normal serum creatinine. Clin Rheumatol. 2010;29(7):729–737.
http://www.ncbi.nlm.nih.gov/pubmed/20174989

56. Rivolta R, Mascagni B, Berruti V, et al. Renal vascular damage in systemic sclerosis patients without clinical evidence of nephropathy. Arthritis Rheum. 1996;39(6):1030–1034.
http://www.ncbi.nlm.nih.gov/pubmed/8651967

57. Steen VD, Syzd A, Johnson JP, Greenberg A, Medsger TA Jr. Kidney disease other than renal crisis in patients with diffuse scleroderma. J Rheumatol. 2005;32(4):649–655.
http://www.ncbi.nlm.nih.gov/pubmed/15801020

58. Trostle DC, Bedetti CD, Steen VD, et al. Renal vascular histology and morphometry in systemic sclerosis. A case-control autopsy study. Arthritis Rheum. 1988;31(3):393–400.
http://www.ncbi.nlm.nih.gov/pubmed/3358801

59. Steen VD, Blair S, Medsger TA Jr. The toxicity of D-penicillamine in systemic sclerosis. Ann Intern Med. 1986;104(5):699–705.
http://www.ncbi.nlm.nih.gov/pubmed/2938530

60. Hall CL. The natural course of gold and penicillamine nephropathy: a longterm study of 54 patients. Adv Exp Med Biol. 1989;252:247–256.
http://www.ncbi.nlm.nih.gov/pubmed/2782197

61. Hall CL, Jawad S, Harrison PR, et al. Natural course of penicillamine ne-phropathy: a long term study of 33 patients. Br Med J (Clin Res Ed). 1988;296 (6629): 1083–1086.
http://www.ncbi.nlm.nih.gov/pubmed/3132218

62. Karpinski J, Jothy S, Radoux V, Levy M, Baran D. D-penicillamine-induced crescentic glomerulonephritis and antimyeloperoxidase antibodies in a patient with scleroderma. Case report and review of the literature. Am J Nephrol. 1997; 17(6):528–532.
http://www.ncbi.nlm.nih.gov/pubmed/9426850

63. Campo A, Mathai SC, Le PJ, et al. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. Am J Respir Crit Care Med. 2010;182(2):252–260.
http://www.ncbi.nlm.nih.gov/pubmed/20339143

64. Bryan C, Knight C, Black CM, Silman AJ. Prediction of f ve-year survival following presentation with scleroderma: development of a simple model using three disease factors at f rst visit. Arthritis Rheum. 1999;42(12):2660–2665.

65. Seiberlich B, Hunzelmann N, Krieg T, Weber M, Schulze-Lohoff E. Intermediate molecular weight proteinuria and albuminuria identify scleroderma patients with increased morbidity. Clin Nephrol. 2008;70(2):110–117.

66. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69(10):1809–1815.
http://www.ncbi.nlm.nih.gov/pubmed/20551155

67. Manno R, Boin F. Immunotherapy of systemic sclerosis. Immunotherapy. 2010;2(6):863–878.
http://www.ncbi.nlm.nih.gov/pubmed/21091117

68. Asano Y. Future treatments in systemic sclerosis. J Dermatol. 2010;37(1):54–70.

69. Milanetti F, Bucha J, Testori A, Burt RK. Autologous hematopoietic stem cell transplantation for systemic sclerosis. Curr Stem Cell Res Ther. 2011; 6(1):16–28. http://www.ncbi.nlm.nih.gov/pubmed/20955159

70. Farge D, Passweg J, van Laar JM, et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. Ann Rheum Dis. 2004;63(8):974–981.

71. McSweeney PA, Nash RA, Sullivan KM, et al. High-dose immunosuppressive therapy for severe systemic sclerosis: initial outcomes. Blood. 2002; 100(5):1602–1610. http://www.ncbi.nlm.nih.gov/pubmed/12176878

72. Nash RA, McSweeney PA, Crofford LJ, et al. High-dose immunosuppres-sive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. Blood. 2007;110(4):1388–1396. http://www.ncbi.nlm.nih.gov/pubmed/17452515

73. Oyama Y, Barr WG, Statkute L, et al. Autologous non-myeloablative hematopoietic stem cell transplantation in patients with systemic sclerosis. Bone Marrow Transplant. 2007;40(6):549–555.

74. Tsukamoto H, Nagafuji K, Horiuchi T, et al. A phase I-II trial of autologous peripheral blood stem cell transplantation in the treatment of refractory autoimmune disease. Ann Rheum Dis. 2006;65(4):508–514. http://www.ncbi.nlm.nih.gov/pubmed/16126798

75. McInnes IB, O'Dell JR. State-of-the-art: rheumatoid arthritis. Ann Rheum Dis. 2010;69(11):1898–1906. http://www.ncbi.nlm.nih.gov/pubmed/20959326

76. Myasoedova E, Davis JM III, Crowson CS, Gabriel SE. Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. Curr Rheumatol Rep. 2010;12(5):379–385. http://www.ncbi.nlm.nih.gov/pubmed/20645137

77. Klarenbeek NB, Kerstens PJ, Huizinga TW, Dijkmans BA, Allaart CF. Recent advances in the management of rheumatoid arthritis. BMJ. 2010;341:c6942.

78. Tak PP, Kalden JR. Advances in rheumatology: new targeted therapeutics. Arthritis Res Ther. 2011;13(Suppl 1):S5.

79. Brun C, Olsen TS, Raaschou F, Sorensen AW. Renal biopsy in rheumatoid arthritis. Nephron. 1965;2(2):65–81.

80. Bulger RJ, Healey LA, Polinsky P. Renal abnormalities in rheumatoid arthritis. Ann Rheum Dis. 1968;27(4):339–344.

81. Karstila K, Korpela M, Sihvonen S, Mustonen J. Prognosis of clinical renal disease and incidence of new renal findings in patients with rheumatoid arthritis: follow-up of a population-based study. Clin Rheumatol. 2007;26(12):2089–2095.

82. Adu D, Berisa F, Howie AJ, et al. Glomerulonephritis in rheumatoid arthritis. Br J Rheumatol. 1993;32(11):1008–1011. http://www.ncbi.nlm.nih.gov/pubmed/8220921

83. Helin HJ, Korpela MM, Mustonen JT, Pasternack AI. Renal biopsy findings and clinicopathologic correlations in rheumatoid arthritis. Arthritis Rheum. 1995;38(2):242–247. http://www.ncbi.nlm.nih.gov/pubmed/7848315

84. Nakano M, Ueno M, Nishi S, et al. Analysis of renal pathology and drug history in 158 Japanese patients with rheumatoid arthritis. Clin Nephrol. 1998;50(3):154–160. http://www.ncbi.nlm.nih.gov/pubmed/9776418

85. Sellars L, Siamopoulos K, Wilkinson R, Leohapand T, Morley AR. Renal biopsy appearances in rheumatoid disease. Clin Nephrol. 1983;20(3):114–120. http://www.ncbi.nlm.nih.gov/pubmed/6627762

86. Kelly CA, Mooney P, Hordon LD, Griffiths ID. Haematuria in rheumatoid arthritis: a follow up study. Ann Rheum Dis. 1988;47(12):993–994. http://www.ncbi.nlm.nih.gov/pubmed/3207389

87. Katz WA, Blodgett RC Jr, Pietrusko RG. Proteinuria in gold-treated rheumatoid arthritis. Ann Intern Med. 1984;101(2):176–179.

88. Honkanen E, Tornroth T, Pettersson E, Skrifvars B. Membranous glomerulonephritis in rheumatoid arthritis not related to gold or D-penicillamine therapy: a report of four cases and review of the literature. Clin Nephrol. 1987;27(2):87–93.

89. Hoshino J, Ubara Y, Hara S, et al. Outcome and treatment of bucillamine-induced nephropathy. Nephron Clin Pract. 2006;104(1):c15–c19.

90. Obayashi M, Uzu T, Harada T, et al. Clinical course of bucillamine-induced nephropathy in patients with rheumatoid arthritis. Clin Exp Nephrol. 2003;7(4):275–278. http://www.ncbi.nlm.nih.gov/pubmed/14712356

91. Samuels B, Lee JC, Engleman EP, Hopper J Jr. Membranous nephropathy in patients with rheumatoid arthritis: relationship to gold therapy. Medicine (Baltimore). 1978;57(4):319–327.

92. Yoshida A, Morozumi K, Takeda A, Koyama K, Oikawa T. Membranous glomerulonephritis in patients with rheumatoid arthritis. Clin Ther. 1994;16(6): 1000–1006.

93. Cohen AS. Amyloidosis associated with rheumatoid arthritis. Med Clin North Am. 1968;52(3):643–653. http://www.ncbi.nlm.nih.gov/pubmed/5653940

94. Koivuniemi R, Paimela L, Suomalainen R, Tornroth T, Leirisalo-Repo M. Amyloidosis is frequently undetected in patients with rheumatoid arthritis. Amyloid. 2008;15(4):262–268. http://www.ncbi.nlm.nih.gov/pubmed/19065298

95. Okuda Y, Yamada T, Matsuura M, Takasugi K, Goto M. Ageing: a risk factor for amyloid A amyloidosis in rheumatoid arthritis. Amyloid. 2011; 18(3):108–111.

96. Immonen K, Finne P, Gronhagen-Riska C, et al. A marked decline in the incidence of renal replacement therapy for amyloidosis associated with inf ammatory rheumatic diseases - data from nationwide registries in Finland. Amyloid. 2011;18(1):25–28.

97. Chevrel G, Jenvrin C, McGregor B, Miossec P. Renal type AA amyloi-dosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. Rheumatology (Oxford). 2001;40(7): 821–825. http://www.ncbi.nlm.nih.gov/pubmed/11477289

98. Nakamura T, Higashi S, Tomoda K, Tsukano M, Baba S. Efficacy of etaner-cept in patients with AA amyloidosis secondary to rheumatoid arthritis. Clin Exp Rheumatol. 2007;25(4):518–522. http://www.ncbi.nlm.nih.gov/pubmed/17888205

99. Nakamura T, Higashi S, Tomoda K, Tsukano M, Shono M. Etanercept can induce resolution of renal deterioration in patients with amyloid A amyloidosis secondary to rheumatoid arthritis. Clin Rheumatol. 2010;29(12):1395–1401.

100. Harada A, Tomita Y, Yamamoto H, et al. Renal amyloidosis associated with crescentic glomerulonephritis. Am J Nephrol. 1984;4(1):52–55. http://www.ncbi.nlm.nih.gov/pubmed/6731501

101. Nagata M, Shimokama T, Harada A, Koyama A, Watanabe T. Glomerular crescents in renal amyloidosis: an epiphenomenon or distinct pathology? Pathol Int. 2001;51(3):179–186. http://www.ncbi.nlm.nih.gov/pubmed/11328533

102. Alonso R, Novoa D, Alonso MC, et al. Nonamyloidotic fibrillar glomerulopathy and rheumatoid arthritis. Nephron. 1993;63(1):120–121.

103. Rosenstock JL, Markowitz GS, Valeri AM, et al. Fibrillary and immunotactoid glomerulonephritis: distinct entities with different clinical and pathologic features. Kidney Int. 2003;63(4):1450–1461.

104. Breedveld FC, Valentijn RM, Westedt ML, Weening JJ. Rapidly progressive glomerulonephritis with glomerular crescent formation in rheumatoid arthritis. Clin Rheumatol. 1985;4(3):353–359.

105. Kuznetsky KA, Schwartz MM, Lohmann LA, Lewis EJ. Necrotizing glomerulonephritis in rheumatoid arthritis. Clin Nephrol. 1986;26(5):257–264. http://www.ncbi.nlm.nih.gov/pubmed/3802589

106. Goto A, Mukai M, Notoya A, Kohno M. Rheumatoid arthritis complicated with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis: a case report. Mod Rheumatol. 2005;15(2):118–122. http://www.ncbi.nlm.nih.gov/pubmed/17029047

107. Messiaen T, M'bappe P, Boffa JJ, et al. MPO-ANCA necrotizing glomerulonephritis related to rheumatoid arthritis. Am J Kidney Dis. 1998;32(5):E6.

108. Mustila A, Korpela M, Mustonen J, et al. Perinuclear antineutrophil cytoplasmic antibody in rheumatoid arthritis: a marker of severe disease with associated nephropathy. Arthritis Rheum. 1997;40(4):710–717. http://www.ncbi.nlm.nih.gov/pubmed/9125254

109. Harper L, Cockwell P, Howie AJ, et al. Focal segmental necrotizing glomerulonephritis in rheumatoid arthritis. QJM. 1997;90(2):125–132.

110. Zhu LJ, Yang X, Yu XQ. Anti-TNF-alpha therapies in systemic lupus erythematosus. J Biomed Biotechnol. 2010;2010:465898.

111. Kaneko K, Nanki T, Hosoya T, Mizoguchi F, Miyasaka N. Etanercept-induced necrotizing crescentic glomerulonephritis in two patients with rheumatoid arthritis. Mod Rheumatol. 2010;20(6):632–636. http://www.ncbi.nlm.nih.gov/pubmed/20617355

112. Simms R, Kipgen D, Dahill S, Marshall D, Rodger RS. ANCA-associated renal vasculitis following anti-tumor necrosis factor alpha therapy. Am J Kidney Dis. 2008;51(3):e11–e14.

113. Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. Nephrol Dial Transplant. 2005;20(7):1400–1406.

114. Fox RI. Sjögren's syndrome. Lancet. 2005;366(9482):321–331. http://www.ncbi.nlm.nih.gov/pubmed/16039337

115. Tzioufas AG, Voulgarelis M. Update on Sjögren's syndrome autoimmune epithelitis: from classification to increased neoplasias. Best Pract Res Clin Rheumatol. 2007;21(6):989–1010. http://www.ncbi.nlm.nih.gov/pubmed/18068857

116. Mavragani CP, Moutsopoulos HM. The geoepidemiology of Sjögren's syndrome. Autoimmun Rev. 2010;9(5):A305–A310.

117. Ng KP, Isenberg DA. Sjögren's syndrome: diagnosis and therapeutic challenges in the elderly. Drugs Aging. 2008;25(1):19–33.
118. Singer NG, Tomanova-Soltys I, Lowe R. Sjögren's syndrome in childhood. Curr Rheumatol Rep. 2008;10(2):147–155.
http://www.ncbi.nlm.nih.gov/pubmed/18460271
119. Lin DF, Yan SM, Zhao Y, et al. Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome. Chin Med J (Engl). 2010;123(22): 3252–3257.
http://www.ncbi.nlm.nih.gov/pubmed/21163125
120. Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjogren's syndrome. Semin Arthritis Rheum. 2000;29(5):296–304.
http://www.ncbi.nlm.nih.gov/pubmed/10805354
121. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classif cation of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum. 1993;36(3):340–347.
http://www.ncbi.nlm.nih.gov/pubmed/8452579
122. Vitali C, Bombardieri S, Jonsson R, et al. Classif cation criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61(6):554–558.
http://www.ncbi.nlm.nih.gov/pubmed/12006334
123. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis. 2010; 69(6):1103–1109.
124. Birnbaum J. Peripheral nervous system manifestations of Sjögren syndrome: clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. Neurologist. 2010;16(5):287–297.
http://www.ncbi.nlm.nih.gov/pubmed/20827117
125. Chai J, Logigian EL. Neurological manifestations of primary Sjögren's syndrome. Curr Opin Neurol. 2010;23(5):509–513.
http://www.ncbi.nlm.nih.gov/pubmed/20689426
126. Hatron PY, Tillie-Leblond I, Launay D, et al. Pulmonary manifestations of Sjögren's syndrome. Presse Med. 2011;40(1Pt2):e49–e64.
127. Papiris SA, Tsonis IA, Moutsopoulos HM. Sjögren's syndrome. Semin Respir Crit Care Med. 2007;28(4):459–471.
http://www.ncbi.nlm.nih.gov/pubmed/17764063
128. Voulgarelis M, Skopouli FN. Clinical, immunologic, and molecular factors predicting lymphoma development in Sjögren's syndrome patients. Clin Rev Allergy Immunol. 2007;32(3):265–274.
129. Voulgarelis M, Tziouf as AG, Moutsopoulos HM. Mortality in Sjögren's syndrome. Clin Exp Rheumatol. 2008;26(5 Suppl 51):S66–S71.
130. Aasarod K, Haga HJ, Berg KJ, Hammerstrom J, Jorstad S. Renal involvement in primary Sjögren's syndrome. QJM. 2000;93(5):297–304.
http://www.ncbi.nlm.nih.gov/pubmed/10825406
131. Bossini N, Savoldi S, Franceschini F, et al. Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. Nephrol Dial Transplant 2001;16(12):2328–2336.
http://www.ncbi.nlm.nih.gov/pubmed/11733624
132. Goules A, Masouridi S, Tziouf as AG, et al. Clinically signif cant and biopsy-documented renal involvement in primary Sjogren syndrome. Medicine (Baltimore). 2000;79(4):241–249.
http://www.ncbi.nlm.nih.gov/pubmed/10941353
133. Maripuri S, Grande JP, Osborn TG, et al. Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009;4(9):1423–1431.
134. Pertovaara M, Korpela M, Kouri T, Pasternack A. The occurrence of renal involvement in primary Sjögren's syndrome: a study of 78 patients. Rheumatology (Oxford). 1999;38(11):1113–1120.
135. Ren H, Wang WM, Chen XN, et al. Renal involvement and followup of 130 patients with primary Sjögren's syndrome. J Rheumatol. 2008;35(2):278–284.
http://www.ncbi.nlm.nih.gov/pubmed/18085734
136. Eriksson P, Denneberg T, Larsson L, Lindstrom F. Biochemical markers of renal disease in primary Sjögren's syndrome. Scand J Urol Nephrol. 1995; 29(4): 383–392.
http://www.ncbi.nlm.nih.gov/pubmed/8719354
137. Pokorny G, Sonkodi S, Ivanyi B et al. Renal involvement in patients with primary Sjögren's syndrome. Scand J Rheumatol. 1989;18(4):231–234.
138. Shiozawa S, Shiozawa K, Shimizu S, Nakada M, Isobe T, Fujita T. Clinical studies of renal disease in Sjögren's syndrome. Ann Rheum Dis. 1987;46(10): 768–772.
139. Siamopoulos KC, Mavridis AK, Elisaf M, Drosos AA, Moutsopoulos HM. Kidney involvement in primary Sjögren's syndrome. Scand J Rheumatol Suppl. 1986;61:156–160.
140. Siamopoulos KC, Elisaf M, Drosos AA, Mavridis AA, Moutsopoulos HM. Renal tubular acidosis in primary Sjögren's syndrome. Clin Rheumatol. 1992;11(2): 226–230.
http://www.ncbi.nlm.nih.gov/pubmed/1617898
141. Viergever PP, Swaak TJ. Renal tubular dysfunction in primary Sjögren's syndrome: clinical studies in 27 patients. Clin Rheumatol. 1991;10(1):23–27.
http://www.ncbi.nlm.nih.gov/pubmed/2065503
142. Vitali C, Tavoni A, Sciuto M, et al. Renal involvement in primary Sjögren's syndrome: a retrospective-prospective study. Scand J Rheumatol. 1991;20(2): 132–136.
http://www.ncbi.nlm.nih.gov/pubmed/2031158
143. Pertovaara M, Korpela M, Pasternack A. Factors predictive of renal involvement in patients with primary Sjögren's syndrome. Clin Nephrol. 2001;56(1):10–18.
http://www.ncbi.nlm.nih.gov/pubmed/11499654
144. Talal N, Zisman E, Schur PH. Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjögren's syndrome. Arthritis Rheum. 1968;11(6): 774–786.
145. Cohen EP, Bastani B, Cohen MR, et al. Absence of H(+)-ATPase in cortical collecting tubules of a patient with Sjögren's syndrome and distal renal tubular acidosis. J Am Soc Nephrol. 1992;3(2):264–271.
http://www.ncbi.nlm.nih.gov/pubmed/1391725
146. DeFranco PE, Haragsim L, Schmitz PG, Bastani B. Absence of vacuolar H(+)-ATPase pump in the collecting duct of a patient with hypokalemic distal renal tubular acidosis and Sjögren's syndrome. J Am Soc Nephrol. 1995;6(2): 295–301.
147. Devuyst O, Lemaire M, Mohebbi N, Wagner CA. Autoantibodies against intercalated cells in Sjögren's syndrome. Kidney Int. 2009;76(2):229.
http://www.ncbi.nlm.nih.gov/pubmed/19564857
148. Han JS, Kim GH, Kim J, et al. Secretory-defect distal renal tubular acidosis is associated with transporter defect in H(+)-ATPase and anion exchanger-1. J Am Soc Nephrol. 2002;13(6):1425–1432.
http://www.ncbi.nlm.nih.gov/pubmed/12039970
149. Bae EH, Han CW, Lee JH, et al. The case. Hypokalemia associated with nephrocalcinosis. Distal renal tubular acidosis associated with Sjögren's syndrome. Kidney Int. 2009;75(4):443–444.
http://www.ncbi.nlm.nih.gov/pubmed/19180156
150. Bastani B, Haragsim L, Gluck S, Siamopoulos KC. Lack of H-ATPase in distal nephron causing hypokalaemic distal RTA in a patient with Sjögren's syndrome. Nephrol Dial Transplant. 1995;10(6):908–909.
http://www.ncbi.nlm.nih.gov/pubmed/7566631
151. Walsh S, Turner CM, Toye A, et al. Immunohistochemical comparison of a case of inherited distal renal tubular acidosis (with a unique AE1 mutation) with an acquired case secondary to autoimmune disease. Nephrol Dial Transplant. 2007;22(3):807–812.
152. Takemoto F, Hoshino J, Sawa N, et al. Autoantibodies against carbonic anhydrase II are increased in renal tubular acidosis associated with Sjögren syndrome. Am J Med. 2005;118(2):181–184.
http://www.ncbi.nlm.nih.gov/pubmed/15694905
153. Takemoto F, Katori H, Sawa N, et al. Induction of anti-carbonic-anhydrase-II antibody causes renal tubular acidosis in a mouse model of Sjögren's syndrome. Nephron Physiol. 2007;106(4):63–68.
http://www.ncbi.nlm.nih.gov/pubmed/17622741
154. Kuwana M, Okano T, Ogawa Y, Kaburaki J, Kawakami Y. Autoantibodies to the amino-terminal fragment of beta-fodrin expressed in glandular epithelial cells in patients with Sjögren's syndrome. J Immunol. 2001;167(9):5449–5456.
http://www.ncbi.nlm.nih.gov/pubmed/11673564
155. Bridoux F, Kyndt X, bou-Ayache R et al. Proximal tubular dysfunction in primary Sjögren's syndrome: a clinicopathological study of 2 cases. Clin Nephrol. 2004;61(6):434–439.
http://www.ncbi.nlm.nih.gov/pubmed/15224808
156. Wang CC, Shiang JC, Huang WT, Lin SH. Hypokalemic paralysis as primary presentation of Fanconi syndrome associated with Sjögren syndrome. J Clin Rheumatol. 2010;16(4):178–180.
157. Kawashima M, Amano T, Morita Y, Yamamura M, Makino H. Hypokalemic paralysis and osteomalacia secondary to renal tubular acidosis in a case with primary Sjögren's syndrome. Mod Rheumatol. 2006;16(1):48–51.
158. Yang YS, Peng CH, Sia SK, Huang CN. Acquired hypophosphatemia osteomalacia associated with Fanconi's syndrome in Sjögren's syndrome. Rheu- matol Int. 2007;27(6):593–597.
http://www.ncbi.nlm.nih.gov/pubmed/17094001
159. Wrong OM, Feest TG, MacIver AG. Immune-related potassium-losing interstitial nephritis: a comparison with distal renal tubular acidosis. Q J Med. 1993;86(8):513–534.
http://www.ncbi.nlm.nih.gov/pubmed/8210309
160. Kaufman I, Schwartz D, Caspi D, Paran D. Sjögren's syndrome - not just Sicca: renal involvement in Sjogren's syndrome. Scand J Rheumatol. 2008;37(3): 213–218.
http://www.ncbi.nlm.nih.gov/pubmed/18465457
161. Soy M, Pamuk ON, Gerenli M, Celik Y. A primary Sjögren's syndrome patient with distal renal tubular acidosis, who presented with symptoms of hy-

pokalemic periodic paralysis: report of a case study and review of the literature. Rheumatol Int. 2005;26(1):86–89.
162. Casatta L, Ferraccioli GF, Bartoli E. Hypokalaemic alkalosis, acquired Gitelman's and Bartter's syndrome in chronic sialoadenitis. Br J Rheumatol. 1997;36(10):1125–1128.
http://www.ncbi.nlm.nih.gov/pubmed/9374934
163. Chen YC, Yang WC, Yang AH, et al. Primary Sjögren's syndrome associated with Gitelman's syndrome presenting with muscular paralysis. Am J Kidney Dis. 2003;42(3):586–590.
http://www.ncbi.nlm.nih.gov/pubmed/12955689
164. Higashi K, Kawaguchi Y, Suzuki K, Nakamura H. Sjögren's syndrome associated with hypokalemic myopathy due to Bartter's syndrome. J Rheumatol. 1997;24(8):1663–1664.
http://www.ncbi.nlm.nih.gov/pubmed/9263176
165. Kim YK, Song HC, Kim WY, et al. Acquired Gitelman syndrome in a patient with primary Sjögren syndrome. Am J Kidney Dis. 2008; 52(6):1163–1167.
166. Pedro-Botet J, Tomas S, Soriano JC, Coll J. Primary Sjögren's syndrome associated with Bartter's syndrome. Clin Exp Rheumatol. 1991;9(2):210–212.
167. Schwarz C, Barisani T, Bauer E, Druml W. A woman with red eyes and hypokalemia: a case of acquired Gitelman syndrome. Wien Klin Wochenschr. 2006;118(7–8):239–242.
http://www.ncbi.nlm.nih.gov/pubmed/16794762
168. Abe H, Tsuboi N, Yukawa S, et al. Thrombotic thrombocytopenic purpura complicating Sjögren's syndrome with crescentic glomerulonephritis and membranous nephritis. Mod Rheumatol. 2004;14(2):174–178.
169. Chen HA, Chen CH, Cheng HH. Hemolytic uremic syndrome and pericarditis as early manifestations of primary Sjögren's syndrome. Clin Rheumatol. 2009;28(Suppl 1):S43–S46.
170. Chen Y, Zhao X, Tang D, et al. IgA nephropathy in two patients with Sjögren's syndrome: one with concomitant autoimmune hepatitis. Intern Med. 2010;49(1):37–43.
http://www.ncbi.nlm.nih.gov/pubmed/20045999
171. Guillot X, Solau-Gervais E, Coulon A, Debiais F. Sjögren's syndrome with ANCA-associated crescentic extramembranous glomerulonephritis. Joint Bone Spine. 2009;76(2):188–189.
http://www.ncbi.nlm.nih.gov/pubmed/19196532
172. Ooms V, Decupere M, Lerut E, Vanrenterghem Y, Kuypers DR. Secondary renal amyloidosis due to long-standing tubulointerstitial nephritis in a patient with Sjögren syndrome. Am J Kidney Dis. 2005;46(5):e75–e80.
173. Tsai TC, Chen CY, Lin WT, Lee WJ, Chen HC. Sjögren's syndrome complicated with IgA nephropathy and leukocytoclastic vasculitis. Ren Fail. 2008;30(7):755–758.
174. Christopher-Stine L, Plotz PH. Adult inflammatory myopathies. Best Pract Res Clin Rheumatol. 2004;18(3):331–344.
http://www.ncbi.nlm.nih.gov/pubmed/15158744
175. Dalakas MC. Review: an update on inflammatory and autoimmune myopathies. Neuropathol Appl Neurobiol. 2011;37(3):226–242.
176. Dimachkie MM. Idiopathic inflammatory myopathies. J Neuroimmunol. 2011;231(1–2):32–42.
http://www.ncbi.nlm.nih.gov/pubmed/21093064
177. Mammen AL. Dermatomyositis and polymyositis: clinical presentation, autoantibodies, and pathogenesis. Ann NY Acad Sci 2010;1184:134–153.
http://www.ncbi.nlm.nih.gov/pubmed/20146695
178. Prieto S, Grau JM. The geoepidemiology of autoimmune muscle disease. Autoimmun Rev. 2010;9(5):A330–A334.
179. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet. 2003;362 (9388):971–982.
http://www.ncbi.nlm.nih.gov/pubmed/14511932
180. Connors GR, Christopher-Stine L, Oddis CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest. 2010;138(6):1464–1474.
http://www.ncbi.nlm.nih.gov/pubmed/21138882
181. Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. Curr Opin Rheumatol. 2010;22(6): 633–638.
182. Kim HW, Choi JR, Jang SJ, et al. Recurrent rhabdomyolysis and myoglobinuric acute renal failure in a patient with polymyositis. Nephrol Dial Transplant. 2005;20(10):2255–2258.
183. Lewington AJ, D'Souza R, Carr S, O'Reilly K, Warwick GL. Polymyositis: a cause of acute renal failure. Nephrol Dial Transplant. 1996;11(4):699–701.
http://www.ncbi.nlm.nih.gov/pubmed/8671863
184. Yen TH, Lai PC, Chen CC, Hsueh S, Huang JY. Renal involvement in patients with polymyositis and dermatomyositis. Int J Clin Pract. 2005;59(2):188–193.
http://www.ncbi.nlm.nih.gov/pubmed/15854195
185. Akashi Y, Inoh M, Gamo N, et al. Dermatomyositis associated with membranous nephropathy in a 43-year-old female. Am J Nephrol. 2002;22(4): 385–388.
186. Frost NA, Morand EF, Hall CL, Maddison PJ, Bhalla AK. Idiopathic polymyositis complicated by arthritis and mesangial proliferative glomerulonephritis: case report and review of the literature. Br J Rheumatol. 1993;32(10):929–931.
187. Takizawa Y, Kanda H, Sato K, et al. Polymyositis associated with focal mesangial proliferative glomerulonephritis with depositions of immune complexes. Clin Rheumatol. 2007;26(5):792–796.
http://www.ncbi.nlm.nih.gov/pubmed/16541204
188. Xie Q, Liu Y, Liu G, Yang N, Yin G. Diffuse proliferative glomerulonephritis associated with dermatomyositis with nephrotic syndrome. Rheumatol Int. 2010;30(6):821–825.
http://www.ncbi.nlm.nih.gov/pubmed/19533141
189. Yen TH, Huang JY, Chen CY. Unexpected IgA nephropathy during the treatment of a young woman with idiopathic dermatomyositis: case report and review of the literature. J Nephrol. 2003;16(1):148–153.
190. Pope JE. Other manifestations of mixed connective tissue disease. Rheum Dis Clin North Am. 2005;31(3):519–533, vii.
http://www.ncbi.nlm.nih.gov/pubmed/16084323
191. Rifkin SI, Gutta H, Nair R, McFarren C, Wheeler DE. Collapsing glomerulopathy in a patient with mixed connective tissue disease. Clin Nephrol. 2011;75(Suppl 1):32–36.
http://www.ncbi.nlm.nih.gov/pubmed/21269591
192. Madan V, Chinoy H, Griffiths CE, Cooper RG. Defining cancer risk in dermatomyositis. Part I. Clin Exp Dermatol. 2009;34(4):451–455.
http://www.ncbi.nlm.nih.gov/pubmed/19522981
193. Buchbinder R, Forbes A, Hall S, Dennett X, Giles G. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. Ann Intern Med. 2001;134(12):1087–1095.
194. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001;357(9250):96–100.
195. Selva-O'Callaghan A, Trallero-Araguas E, Grau-Junyent JM, Labrador-Horrillo M. Malignancy and myositis: novel autoantibodies and new insights. Curr Opin Rheumatol. 2010;22(6):627–632.